

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208547Orig1s000**

**MEDICAL REVIEW(S)**

Clinical Review

Cindy Welsh

NDA 208547

(b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection)

### CLINICAL REVIEW

<b>Application Type</b>	NDA
<b>Application Number(s)</b>	208547
<b>Priority or Standard</b>	Priority
<b>Submit Date(s)</b>	7/1/15
<b>Received Date(s)</b>	7/1/15
<b>PDUFA Goal Date</b>	3/1/16
<b>Division/Office</b>	DMIP/ODEIV/OND
<b>Reviewer Name(s)</b>	Cindy Welsh
<b>Review Completion Date</b>	12/4/15
<b>Established Name</b>	Kit for the Preparation of 68Ga-DOTATATE for Injection
<b>(Proposed) Trade Name</b>	(b) (4) (to be changed based upon DMEPA review, final name pending at time of filing this review)
<b>Applicant</b>	Advanced Accelerator Applications (AAA)
<b>Formulation(s)</b>	Intravenous Injection
<b>Dosing Regimen</b>	2 MBq/kg of body weight (0.054 mCi/kg)
<b>Applicant Proposed Indication(s)/Population(s)</b>	(b) (4)
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	A kit for the preparation of 68Ga-DOTATATE indicated for positron emission tomography (PET) imaging, as an adjunct to other diagnostic tests, in the localization of neuroendocrine tumors (NETs) in adult and pediatric patients (the indication statement being proposed by this reviewer differs from the one proposed by the applicant and may differ from the one that would be approved)

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## Glossary

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AAA	Advanced Accelerator Applications
AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	conventional imaging
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CT	Computed tomography
DMC	data monitoring committee
DWMRI	diffusion weighted MRI
ECG	electrocardiogram
eCTD	electronic common technical document
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
ETASU	elements to assure safe use
EU	European Union

CDER Clinical Review Template 2015 Edition

Version date: June 25, 2015 for initial rollout (NME/original BLA reviews)

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F18	Fluorine 18 isotope
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FN	false negative
FP	false positive
Ga68	Gallium 68 isotope
GCP	good clinical practice
GEP	gastro-entero-pancreatic
GRMP	good review management practice
Gy	gray
ICH	International Conference on Harmonization
111 In	indium 111 isotope
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
Kg	kilogram
MBq	Megabecquerel
mCi	millicurie
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRI	magnetic resonance imaging
mSv	milliseivert
NANETS	North American Neuroendocrine Tumor Society
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NED	no evidence of disease
NET	neuroendocrine tumor
NME	new molecular entity
NOC	DOTANOC
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PET	Positron emission tomography
PI	prescribing information
PK	pharmacokinetics

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PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
Rem	Roentgen equivalent man
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SEER	Surveillance, Epidemiology, and End Results
SGE	special government employee
SOC	standard of care
SPECT	single photon emission computed tomography
SSTR2	somatostatin receptor 2
TEAE	treatment emergent adverse event
Tc99m	technetium 99m isotope
TOC	DOTATOC
US	United States
VUMC	Vanderbilt University Medical Center

# 1

## 1 Executive Summary

---

### 1.1. Product Introduction

(b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection) (68Ga-DOTATATE), an NME, is a radioactive diagnostic PET agent indicated, as proposed by the applicant, (b) (4). The recommended radioactivity to be administered by intravenous injection (bolus) is 2 MBq/kg of body weight (0.054 mCi/kg), (b) (4) not more than 200 MBq (5.4 mCi).

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The application contains sufficient evidence based upon the totality of the data contained within the submitted literature and VUMC clinical trial that the drug has been shown to be effective as a diagnostic radiopharmaceutical for the NET population. In comparison to the radiodiagnostic agent currently available for use in this patient population, PET with 68Ga-DOTATATE results in lower radiation exposure to the patient, convenience for the staff and the patients with respect to decreased time required for imaging procedures, and images with increased resolution.

### 1.3. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

Ga68 DOTATATE PET is indicated as an adjunct to other diagnostic imaging tests in patients with NETs for localization of disease. The product should be approved.

NETs are a heterogeneous group of malignancies that may be life-threatening particularly for those patients with pancreatic primary sites and poorly differentiated disease. The current diagnostic imaging assessment includes anatomical imaging and SPECT. The limitation of the SPECT is that it requires ~2 days to acquire the appropriate images and has poor resolution.

The submitted evidence describes the benefit of the product in terms of increased sensitivity without a decrease in specificity, improved image resolution, decreased imaging time, and decreased radiation dose to the patient. This product should serve as an adjunct to other imaging modalities for localization of disease. This test may not be useful in patients with poorly differentiated tumors that do not have or have lost expression of the SSTRs as can occur in poorly differentiated tumors.

There are no reported AEs in the literature or in the clinical data submitted. The mass dose of the active moiety is sub-pharmacologic. There is no evidence to suggest that the safety profile will change in the post market setting.

It is expected that the product should be able to serve the NET population for disease localization in a fashion similar to the currently approved product but with decreased imaging time, decreased radiation dose, and increased image resolution without introduction of safety concerns.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u><a href="#">Analysis of Condition</a></u>	<ul style="list-style-type: none"><li>NETs are a rare (~350 cases/million), heterogeneous group of malignancies arising in a variety tissues originating from neuroendocrine cells that present with variable clinical manifestations due to the peptides that are secreted. The clinical course may be indolent or in</li></ul>	NETs are life-threatening conditions that frequently have fatal outcomes. 5 year survival rates vary from ~10% - 100% depending upon site of origin and degree of differentiation. The

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>some cases quite progressive resulting in death at 5 years. There is a small percentage of the pediatric population who may develop an NET or have a neuroblastoma (not an NET) that expresses SSTRs.</p>	<p>majority fall within the 50-90% 5 year survival range. There is no data to suggest that this product would differ in its ability to localize disease in the pediatric population.</p>
<p><a href="#">Current Treatment Options</a></p>	<ul style="list-style-type: none"> <li>Current diagnostic imaging options for somatostatin receptor positive NETs include anatomical imaging and SPECT. The SPECT imaging is usually conducted after anatomical imaging. In patients who have poorly differentiated tumors with loss of the SSR, the SPECT will be negative yet a F18 FDG PET is likely to be positive for disease. The SPECT procedure requires ~2 days for imaging and has poor resolution.</li> </ul>	<p>The patient population will benefit from this product due to the decreased radiation dose to the patient, shorter scan time requirements, and improved image resolution.</p>
<p><a href="#">Benefit</a></p>	<ul style="list-style-type: none"> <li>The sponsor conducted a literature review to support the use of the product and compared it to the currently approved product for the same indication and patient population. The number of articles is small, the number of patients is small, and the articles are not detailed nor are they prospective and blinded to meet the rigor of a traditional clinical trial. The submitted clinical data were obtained on the basis of a protocol which was originally not intended for drug development. The statistical plan was not written a priori. However, the patients were enrolled prospectively and the images were read in a blinded fashion and compared to the currently approved product. In both sets of evidence, literature and the clinical data, the product had greater sensitivity. There was no difference in the specificity but it is difficult to draw any conclusions given the patient population studied (insufficient patients enrolled without the disease). The product may provide diagnostic</li> </ul>	<p>The submitted information supports the use of this product as a complementary diagnostic imaging test. The patient may receive previously unknown information about the extent of their disease, lower radiation dose, shorter imaging time, and better image resolution.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>information regarding the localization of the patient’s disease that may not be noted on other imaging modalities (i.e. it is complementary to the existing diagnostic armamentarium). Compared to the SPECT scan, the PET scan offers a decreased radiation dose to the patient, shorter duration of the imaging time, and greater image resolution.</p>	
<p><u>Risk</u></p>	<ul style="list-style-type: none"> <li>There are ~1400 patients reported in the literature to have received this product. Unfortunately, the literature has not provided detailed reports of AEs. The mass dose of the drug is sub-pharmacologic and the radiation dose is less than that of the approved product for the same patient population and indication. There are no AEs found in the literature or in the VUMC clinical trial experience associated with this product. The articles reviewed for the pediatric population did not identify pediatric safety concerns.</li> </ul>	<p>No quantifiable risk. No AEs noted. There is no expectation that the risk profile will change in the post marketing setting.</p>
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> <li>No risk management issues were identified in the drug development program.</li> </ul>	<p>There are no risk management issues as there are no safety signals associated with this product development.</p>

## 2 Therapeutic Context

### 2.1. Analysis of Condition

The proposed indication for this application is PET imaging of NETs. The disease is a rare (350 cases/million population) heterogeneous group of malignancies that arise from neuroendocrine cells and present with a variety of signs and symptoms that may impact quality and quantity of life depending upon the secreted peptide involved. 5 year survival rates can vary from a low of ~7% to approaching 100% depending upon the primary site of origin and the degree of differentiation.

### 2.2. Analysis of Current Treatment Options

Diagnostic image currently used in this disease include OctreoScan (the currently approved product for the same patient population and indication detailed in the table below) and conventional anatomical imaging (CT, MRI, US) that is not specifically labeled for this disease. For tumors that do not have SSTRs or have lost their SSTRs (e.g. poorly differentiated tumors), F18 PET may be useful but not specifically indicated for this disease but for malignancy in general.

**Table 1: Summary of Diagnostic Armamentarium Relevant to Proposed Indication**

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Diagnostic Radiopharmaceutical Agents						
OctreoScan In-111 Pentetreotide  <i>Information in this table was extracted from the approved label</i>	A radio-pharmaceutical agent for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors	1994	The recommended intravenous dose for planar imaging is 111 MBq (3.0 mCi).  The recommended intravenous dose for SPECT imaging is 222 MBq (6.0 mCi).	OctreoScan results were consistent with the final diagnosis (success) in 267 of 309 evaluable patients (86.4%).  OctreoScan success was observed in 27 of 32 patients (84.4%) with clinically nonfunctioning neuro endocrine tumors (i.e., no symptom of a	The following adverse effects were observed in clinical trials at a frequency of < 1% of 538 patients: dizziness, fever, flush, headache, hypotension changes in liver	Effective Dose Equivalent:  Planar – 13.03 mSv/111 MBq or 1.3 rem/3 mCi  SPECT – 26.06 mSv/222 MBq or 2.61 rem/6 mCi  Label does

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				<p>clinical syndrome mediated by abnormally elevated hormones).</p> <p>OctreoScan localized previously unidentified tumors in 57/204 patients. In 55/195 patients, indium In 111 pentetreotide uptake occurred in lesions not thought to have somatostatin receptors. In a small subgroup of 39 patients who had tissue confirmation, the sensitivity rate for OctreoScan scintigraphy was 85.7%; for CT/MRI the rate was 68%. The specificity rate for OctreoScan scintigraphy was 50%, the rate for CT/MRI was 12%. Larger studies are needed to confirm these comparisons. Overall, including all tumor types with or without the presence of somatostatin receptors, there were 3/508 false positives and 104/508 false negatives.</p>	<p>enzymes, joint pain, nausea, sweating, and weakness. These adverse effects were transient.</p> <p>In clinical trials, there was one reported case of bradycardia and one case of decreased hematocrit and hemoglobin.</p>	<p>not address imaging times. Routine imaging may take 2 days</p>
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2015 NCCN Guidelines:

- Do not recommend somatostatin scintigraphy and FDG PET for routine surveillance

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- Somatostatin scintigraphy may be appropriate for initial diagnosis
- Somatostatin scintigraphy may be indicated to assess disease location and burden for comparison in cases of possible recurrence
- Consider somatostatin scintigraphy for somatostatin + tumors when considering treatment with a somatostatin analog

### 2014 NANETS Guidelines

- Recommended for initial diagnosis for most subtypes of NET
- Considered for follow up

### 2012 ESMO Guidelines

- Preoperative staging should, whenever possible, include somatostatin receptor scintigraphy which can be replaced by 68Gallium-DOTA-TOC/-NOC/-TATE PET with higher spatial resolution and quantification, which causes higher sensitivity and specificity

## 3 Regulatory Background

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### 3.1. U.S. Regulatory Actions and Marketing History

This drug is an NME and is not currently marketed in the U.S.

### 3.2. Summary of Presubmission/Submission Regulatory Activity

(b) (4) drug development was conducted under IND 122818.

The clinical data from VUMC was conducted under IND 111972.

Note that there are a number of diagnostic PET INDs for the same (DOTATATE) and similar products (DOTATOC and DOTANOC) from competing sponsors with the same isotope (Ga68) under development that bind to SSTRs and would be used in the same patient population. The majority of these are academic institutions also using expanded access protocols (many are identical) with request to charge submissions.

(b) (4)

(b) (4) It is reasonable to assume that the Ga68 DOTATATE PET would be used to identify patients with SST2 receptor (+) disease who would be candidates for these therapeutic products as well as be used to follow the response to these therapies similar to how F18 FDG PET may be used in some diseases. (b) (4)

(b) (4)

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(b) (4)

#### Meetings:

- 7/1/14: DMIP agreed that the sponsor could submit an NDA based upon literature, preferably meta-analysis if there are sufficient data, if not, a systematic review would be acceptable, and supported by the results of the expanded access study conducted at Vanderbilt University Medical Center. However, if the literature was found to be insufficient then the sponsor would need to conduct a clinical trial as noted in the meeting minutes:
  - “In general, for your IND and eventual NDA, evidence of safety and efficacy may be based on literature with supportive data supplied by the already completed VUMC study.” And
  - “If the literature based data are insufficient we recommend conducting a clinical trial in a clinically relevant patient population.”
- 11/19/14: DMIP provided advice on the methodology of the meta-analysis/systematic review, toxicity scale, endpoints, and the statistical analysis plan.

#### Orphan drug:

- FDA (Designation Request 13/4136)
- EMA (EMA/OD/152/13)

Breakthrough: no application submitted

Fast track: no

Priority review: yes – determined at time of NDA submission

### 3.3. Foreign Regulatory Actions and Marketing History

There is no foreign marketing experience. The product has orphan designation by the EMA. The product is available via compassionate use in Germany.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

An OSI audit was not requested for the literature review. The results of the OSI data confirmation were not available at the time of this review

#### Product Quality

The CMC review is ongoing. There were multiple IRs sent to the sponsor that are being evaluated. There are important documents that are awaiting translation. The CMC review team has decided not to inspect the (b) (4) manufacturing site as it does not manufacture the drug

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product.

#### 4.2. **Clinical Microbiology**

None.

#### 4.3. **Nonclinical Pharmacology/Toxicology**

No issues were identified.

#### 4.4. **Clinical Pharmacology**

Non-radioactive somatostatin analogs competitively bind to SSTR2. The package insert recommends avoiding concomitant treatment with long acting analogs of somatostatin (b) (4), and short acting analogs for 24 hours prior.

The effective radiation dose (exposure to patients) resulting from the administration of 68Ga-DOTA0-Tyr3-Octreotate PET is much lower than that resulting from administration of 111In-pentetreotide. The effective radiation dose resulting from the administration of 150 MBq for an adult weighing 75 kg, is about 3.15 mSv as compared to 26 mSv for 222 MBq dose approved for 111In-pentetreotide for Single Photon Emission Computed Tomography (SPECT) imaging.

#### 4.4.1. Mechanism of Action

The product has a high affinity for and binds to cells that express the SSTR2 that are found in neuroendocrine tumors.

#### 4.4.2. Pharmacodynamics

The product is administered in microgram amounts (<50) and no pharmacologic action is expected.

#### 4.4.3. Pharmacokinetics

Ga68 has a 68 minute half-life. Peak tumor uptake is ~70 minutes post injection. Elimination is via the urinary system. It has not been studied in patients with renal or hepatic impairment or pediatric patients.

Normal biodistribution shows uptake in the SSTR2-expressing organs such as pituitary, thyroid, stomach wall, spleen, adrenals, kidneys, pancreas and prostate and in the liver and salivary glands, with excreted activity in the bowel, the kidneys and urinary bladder. Uptake by uncinatate process of pancreas may be seen in ~12% patients (false positive) and should be taken into consideration while interpreting the findings in this anatomical area. Other reasons for potential false positive interpretation include meningioma, fibrous dysplasia, breast fibroadenoma, postsurgical inflammation, reactive lymph nodes, arthritis and accessory spleen.

#### 4.5. Devices and Companion Diagnostic Issues

Not applicable.

#### 4.6. Consumer Study Reviews

Not applicable.

## 5 Sources of Clinical Data and Review Strategy

### 5.1. Table of Clinical Studies

**Table 2 Listing of Clinical Trials Relevant to this NDA**

<b>Trial Identity</b>	<b>Trial Design</b>	<b>Regimen/ schedule/ route</b>	<b>Study Endpoints</b>	<b>No. of patients enrolled</b>	<b>Study Population</b>
<b><i>Literature to Support Efficacy compared to OctreoScan</i></b>					
Literature review	Systematic review	variable	variable	n/a	primary or metastatic NETs predominantly GEP
<b><i>Other studies pertinent to the review of efficacy and safety</i></b>					
VUMC	Phase 2, single center, open-label, prospective and blinded PET scan reading followed by comparison to standard imaging	5-7 mCi 50 ug IV x 1	1. Sensitivity Specificity 2. Impact on patient management compared to conventional imaging	97	primary or metastatic NETs predominantly GEP

## 5.2. Review Strategy

This reviewer assessed the systematic review protocol and corresponding articles submitted as literature to support the product approval. This reviewer chose to focus primarily upon the comparison of efficacy of the Ga68 DOTATATE PET to the currently approved product, OctreoScan, for the same patient population (NET) and similar indication. Additionally, the expanded access protocol and study report including tabulated results from the VUMC trial were reviewed. The sponsor's information will be presented and followed by my commentary where appropriate. The sponsor did not seek a pediatric indication nor did they submit pediatric data. This reviewer conducted a PubMed search and found 3 articles related to use of this product in the pediatric population. They are discussed in section 7. 1.3. Also reviewed were the 2015 NCCN guidelines, the 2013 NANETS guidelines, and the 2012 ESMO clinical practice guidelines for imaging recommendations (see section 2.2). Note that many of the figures and tables found in sections 6 and 7 were reproduced from the supportive literature or the sponsor submission and may not be numbered sequentially.

Note: at the time of filing this review the sponsor has not yet responded to an IR regarding the additional data requested from the VUMC clinical site. Should review of the information submitted in response to the IR change the approvability or impact the reviewer's opinion of the use of this product, this review will be amended. Furthermore, the indication statement has not been finalized.

There are multiple sections of this reviewer template that are not applicable to the review of this product due to the limited prevalence of the disease (i.e. Orphan status), the microgram sub-pharmacologic amount of product, the short half-life of the product allowing for on-site production, and the unique regulations surrounding PET products that has resulted in the widespread use and adoption of the product as standard of care in the US and the EU.

## 6 Review of Relevant Individual Trials Used to Support Efficacy

### 6.1. 68Ga-DOTATATE compared to 111In-octreotide imaging for pulmonary and GEP NET with PET/CT: A systematic review and meta-analysis

#### 6.1.1. Study Design

##### Overview and Objective

68Ga-DOTATATE compared to 111In-octreotide imaging for pulmonary and GEP NET with

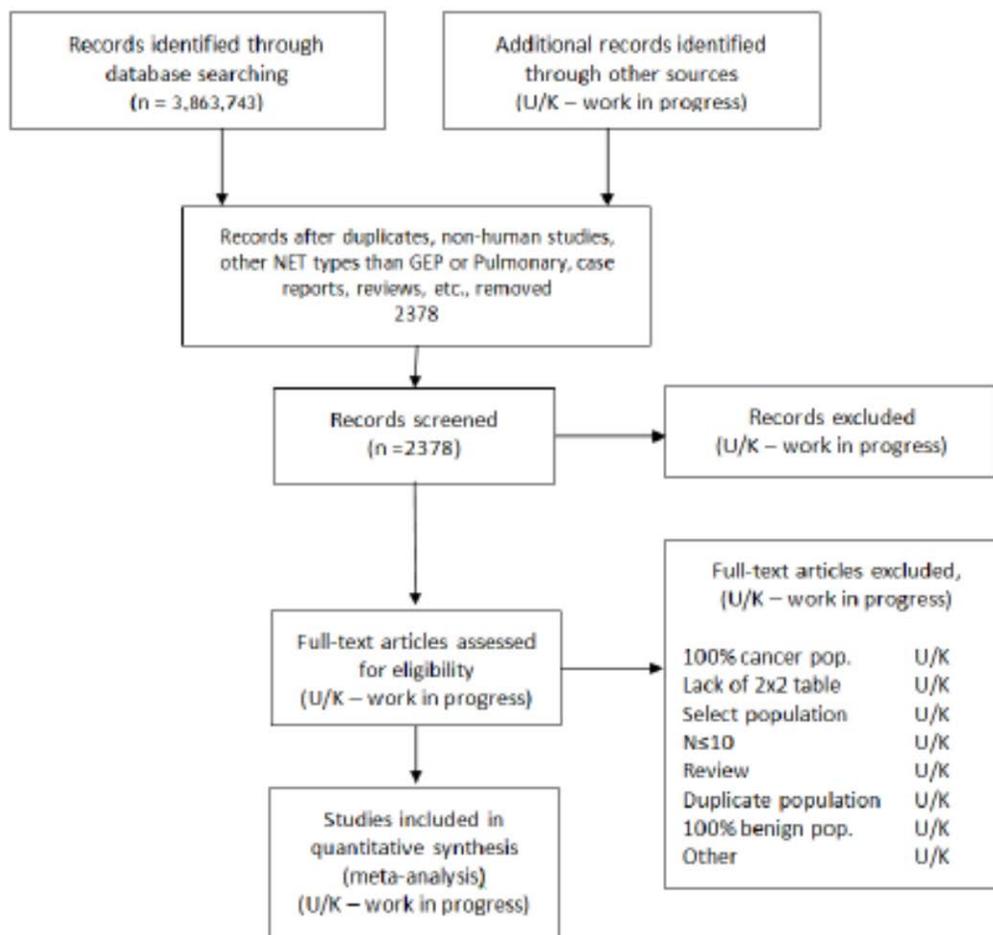
PET/CT: A systematic review and meta-analysis. In this trial the sponsor attempts to provide efficacy and safety data from the available literature to support a regulatory pathway forward for marketing of the product that is already considered standard of care in the NET community of patients and physicians in the US and EU.

### Trial Design

See the figure below excerpted from the NDA submission for an overview of the literature review design.

Figure 1: Literature review design

### Prisma Flow Diagram – <sup>68</sup>Ga-DOTATATE PET/CT: (U/K = unknown)



The sponsor utilized known techniques for conducting the literature search (PRISMA guidelines and PICOS method) and assessment of the articles (e.g. QUADAS).

- The inclusion criteria were prespecified and CRFs for data extraction prepared

- the typical databases (Medline, EMBASE, and Cochrane Reviews) were searched
- the approved product (OctreoScan) was the preferred comparator although conventional imaging (CT/MRI) was also allowed
- histopathology as a truth standard was preferred but not required
- blinded image interpretation in a prospective fashion preferred

### Study Endpoints

The sponsor chose the currently FDA approved test, OctreoScan, as the comparator assessing its performance in terms of sensitivity and specificity as the primary endpoint as compared to a standard of truth (conventional imaging). The division agreed to the use of OctreoScan as the comparator and a non-inferiority endpoint. Change in patient management was chosen as a secondary endpoint.

### Statistical Analysis Plan

Missing data was not replaced. There was no interim analysis or adjustment for multiplicity. The efficacy variables used the following table:

Figure 2: Statistical plan design

		Standard of truth	
		Disease Positives (DP)	Disease Negatives (DN)
Imaging procedure (either 68Ga-DOTATATE or 111In-octreotide)	Imaging Positives (IP)	True positives (TP)	False Negatives (FN)
	Imaging Negatives (IN)	False positives (FP)	True Negatives (TN)

### Protocol Amendments

Not applicable.

### Data Quality and Integrity: Sponsor's Assurance

Not applicable to this literature review.

### 6.1.2. Study Results

### Compliance with Good Clinical Practices

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Not applicable for this 505(b)(2) application.

### **Financial Disclosure**

Financial disclosure was submitted from the investigators at VUMC. None of the investigators has a financial interest in the drug development program for this product. The remainder of the data was taken from published articles that are readily available in the public domain.

### **Patient Disposition**

Not applicable to this 505(b)(2) application.

### **Protocol Violations/Deviations**

Not applicable to this 505(b)(2) application.

### **Table of Demographic Characteristics**

Not applicable to this 505(b)(2) application.

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APPEARS THIS WAY ON ORIGINAL

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Not applicable to this 505(b)(2) application.

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Not applicable to this 505(b)(2) application.

**Efficacy Results – Primary Endpoint**

Note: The original intent was to conduct and report a meta-analysis. The meta-analysis was not conducted as the prespecified minimum number of comparative articles (10) that met the inclusion criteria was not found. The efficacy of the product was addressed by the information found below that was selected from the sponsor's submission by the reviewer.

**Ga68 DOTATATE vs. 111In pentetreotide (OctreoScan)**

*Retrospective studies with blinded reads*

*Note: There are no prospective, blinded clinical trials or articles [comparing Ga68 DOTATATE to OctreoScan, the currently approved product.](#)*

*Figure 3: Comparative studies PET vs. SPECT*

Study Country	Quality Score	Number of patients	Study type	Blinding	Patient Population
<b>Studies comparing <sup>68</sup>Ga-DOTATATE to <sup>111</sup>In-DTPA-Octreotide</b>					
<a href="#">Srirajaskanthan 2010 UK</a>	7	51	Retrospective	Blinded	Chosen after negative or equivocal <sup>111</sup> In-DTPA-Octreotide scan.
<a href="#">Hofman 2012 Australia</a>	8	59	Retrospective	Blinded	Based on clinical need. 52 proven or suspected GEP or bronchial NETs and 7 neural crest/mesenchymal tumors.

**Srirajaskanthan et.al. [J Nucl Med 2010; 51:875–882]**

*The patients were prospectively followed in NET unit but the scans were retrospectively reviewed.*

**N=51 NET (histologically proven) patients with negative or low grade uptake on 111 In-pentetreotide scan**

- Scans and clinical data were retrospectively reviewed
- Histopathology available presumably from original diagnosis
- 200 MBq of 111 In-pentetreotide (2 readers; discrepancies resolved via consensus)
- 120–200 MBq of 68Ga-DOTATATE (2 readers blinded to 111-In scan results)
- 1-8 months between scans (median 4 months)
- Scan techniques available in article
- Standard of care CT and/or MR imaging used as comparison

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- The images from 68Ga-DOTATATE PET/CT were reported in consensus by 2 physicians who were unaware of the results of the previous 111In-DTPA-octreotide study.

### Image interpretation

- Lesion counting broken down into organ, nodes, musculoskeletal
- Because of confluence and inability to clearly delineate single liver lesions in some cases, liver metastases were classified as 1 organ metastasis, independent of the number of liver metastases present. Lymph nodes smaller than 1 cm on CT or MRI and showing marked avidity for 68Ga-DOTATATE and 111In-DTPAoctreotide were labeled as positive for disease.

### Results

51 patients (ages 18-80 years) underwent 111-In SPECT and 68-Ga PET scans. PET imaging was conducted between January 2007 and April 2008 using 120–200 MBq. Somatostatin analogs were not withdrawn in the 27 patients receiving this medication prior to undergoing PET.

- 47/51 patients had disease on cross sectional imaging and 4/51 patients were post op and had surveillance cross sectional imaging (i.e. no evidence of disease [NED])
  - 226 lesions on cross sectional anatomical imaging in the 47 patients with disease
  - 35/51 negative indium scan
    - 3/35 are NED based on anatomical imaging and labs
    - 32/35 had + anatomical imaging (125 lesions)
    - 27/32 had + Ga-68 detecting 97 lesions
  - 16/51 had 27 lesions on indium scan (faint uptake)
- 68Ga-DOTATATE PET identified disease in 41 of 47 patients (87.2%) and detected 168 (74.3%) of the 226 lesions identified on cross-sectional imaging.
- Five patients who were negative for (disease) uptake on both 68Ga-DOTATATE PET and 111In-DOTA-octreotide scanning had evidence of disease on cross-sectional imaging. In these patients, 27 metastatic lesions were identified on CT +/- MRI.
  - Histologic results (it is assumed that the histology is from the original diagnosis and not from post PET imaging biopsy) from these 5 patients showed 2 with low grade tumors, 2 with intermediate-grade tumors, and 1 with a high-grade tumor.
- Of the 16 patients with low grade or faint uptake on 111-In scan, 15 had + anatomical imaging (101 lesions).
  - 1 patient had a false + 111-In scan result (post-operative with negative markers); the Ga-68 scan was negative (true negative)
  - 14/16 had uptake on 68Ga-DOTATATE PET

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- 101 lesions were identified with cross-sectional imaging in the 15 patients with disease; of these, 71 (70.3%) were identified with 68Ga-DOTATATE PET.
- **1/16 Ga-68 was false negative (pancreatic)**

*Reviewer's comment: The overall assessment, in reference to PET performance in this study, is that among NET patients with negative or inconclusive SPECT imaging and positive anatomic imaging, Ga68-DOTATATE PET localized at least 1 lesion in 96% of the patients and 74% of all lesions identified in these patients by anatomic imaging.*

*Change in Patient Management*

- 36/51 patients had a change in management post Ga-68 PET
  - 20 were suitable for peptide receptor radio-targeted therapy with 90Y-DOTATATE (*which is an investigational therapy*)
  - 4 patients with negative results on both 68Ga and 111In scans were excluded from peptide receptor therapy with 90Y-DOTATATE
  - 7 patients without functional symptoms but positive for uptake on 68Ga, somatostatin analogs were commenced for their antiproliferative effects.
  - 4 patients surgery was regarded as a possible treatment option because of the presence of limited and resectable disease.
    - 3 patients, the disease was localized to the abdomen and pelvis
    - 1 patient, the disease was limited to the liver.
    - 68Ga changed clinical management by confirming that the disease shown on cross-sectional PET had not been identified on 111In scan.
  - 1 patient NED CT or biochemically, low-grade uptake in the mediastinum and left lung was observed on the 111In scan. 68Ga was negative and the patient was regarded as disease free. In this patient, 68Ga PET confirmed cross-sectional imaging findings but altered management by finding no evidence of the uptake that had been seen on 111In scan.

*Reviewer comment:*

*The patient population in this article is a selected subset with negative or low uptake OctreoScan.*

*The article states:*

“The purpose of our study was not to directly compare the performance of 111In-DTPA-octreotide scintigraphy and 68Ga-DOTATATE PET but to assess the clinical utility of 68Ga-DOTATATE PET/CT in a specific subset with no uptake or low-grade uptake on 111In-DTPA octreotide scintigraphy.”

*However, the majority of the article discussed lesion detection.* (b) (4)

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(b) (4)

(b) (4)

**Hofman et al. High management impact of Ga-68dotatate (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. J Med Imaging Radiat Oncol 2012;56:40-7**

N=59 patients (76 studies – extra scans for response to PRRT and not included in analysis); potentially resectable based on 111-In or on clinical evidence of NET but (-) 111-In scan or patients with widely metastatic disease but no evidence of primary site; 40/59 patients had prior 111-In scan; no pediatric cases; retrospective review of images – order unclear; management impact as defined by the sponsor as high, moderate or low was determined by clinical review and follow up to assess pre-PET stage, treatment intent and post-PET management change; blinded scoring of the number of abnormalities (1, 2–5 or >5) within a particular organ/region (detection of additional lesions were not considered to constitute ‘additional information’);

Ga-68 provided additional information in:

- 68% (40/59) of cases compared to conventional imaging (CT/MRI/US/bone scan)
  - In 33 of 59 (56%), this related to identification of disease in an additional organ or distant nodal disease
- 83% (33/40) of cases compared to 111-In scan
- 5 patients were determined to be surgical candidates based upon Ga68PET.
  - 4/5 patients had histologic confirmation
  - 1/5 patients had negative histology (**false positive Ga68 PET**)

Low PET impact=24

In patients with previous 111-In scan change in management:

- < 30 months between SPECT and PET scans 71% change
- 3-6 months between SPECT and PET scans 40% change
- > 6 months between SPECT and PET scans 50% change

The most common change was to increase the number of lesions detected leading to systemic therapy rather than surgery.

*Reviewer comment:* (b) (4)

(b) (4)

## Efficacy compared to conventional imaging (2 articles)

Prospective studies with blinded reads PET vs. CI.

Figure 4: Comparative studies PET vs. CI

Study Country	Quality Score	Number of patients	Study type	Blinding	Patient Population
<b>Studies comparing <sup>68</sup>Ga-DOTATATE to conventional imaging</b>					
<a href="#">Wild 2013 UK</a>	11	18	Prospective	Blinded	Biopsy-proven metastatic GEP with CT or MRI imaging also available from long-term surveillance.
<a href="#">Etchebehere 2014 Brazil</a>	8	19	Prospective	Blinded	Patients with histologically determined NETs with suspected recurrence.

**2013 Wild** Comparison of 68Ga-DOTANOC and 68Ga-DOTATATE PET/CT Within Patients with Gastroenteropancreatic Neuroendocrine Tumors J Nucl Med 2013; 54:364–372 DOI: 10.2967/jnumed.112.111724

Prospective, single center, comparing –TATE and –NOC, cross over design in random order from patients followed in an NET clinic

- N=18 adults; no pediatric patients
- Scan conducted for staging or re-staging
- CI (CT / MRI / or FDG-PET) conducted as standard of care and utilized as standard of truth
- somatostatin analogs were discontinued prior to scans
- 155 MBq (range 135-170 MBq)
- 2 independent readers blinded to type of scan, results of other imaging

### Results

#### Patient level

17/18 PET + (94% sensitivity)

1/18 PET (-); high-grade NET

2/18 had uptake in pancreatic uncinuate region that was not confirmed by CI; 1 in prostate

#### Lesion level

212/248 (85%) sensitivity

Specificity not addressed

#### Change in management

Not discussed for -TATE

#### Safety

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No AEs reported

### Limitations

1. Very small population
2. Patient level data not detailed
3. No mention of changes in management due to –TATE scans. Presumably, the FP uptake in the uncinated pancreas and the prostate did not affect the overall patient status.

### Recommendation

*Reviewer comment: The article supports the use of Ga68 PET as an adjunct to other diagnostic tests in this orphan population similar to other diagnostic agents that have been approved as noted in the recommendation for the article above.* (b) (4)

### **2014 Etchebehere 68Ga-DOTATATE PET/CT, 99mTc-HYNIC-Octreotide SPECT/CT, and Whole-Body MR Imaging in Detection of Neuroendocrine Tumors: A Prospective Trial J Nucl Med 2014; 55:1598–1604. DOI: 10.2967/jnumed.114.144543**

- N=19 consecutive, prospective, adult patients with suspected recurrence of NET
- Imaging included Tc99m HYNIC-octreotide SPECT, PET, and DW-MRI within 3 months
- PET 5 mCi dose (185 MBq)
- 3 teams of readers blinded to the other imaging analyzed the images separately (order not specified)
- Images assessed at the lesion level
- Somatostatin analog treatment was withheld prior to scanning (24 hours for short acting; 4 weeks after last dose of long acting)
- Standard of truth: consensus among investigators at the end of the study evaluating all lesions by all methods, clinical follow-up, and biopsy of suggestive lesions when possible.

### Results

- 1 FP PET uptake noted in the uncinated process of the pancreas
- FN on PET and SPECT but not on MRI
  - Lung nodules close to the liver dome were (# not specified)
  - Enlarged hepatogastric lymph node (1)
- See overall performance in the table below taken from the article  
Figure 5: Performance SPECT vs. PET vs. MRI

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**TABLE 2**  
Performance of SSRS SPECT/CT, <sup>68</sup>Ga-DOTATATE PET/CT, and WB DWI According to Sites

Organ type	Imaging modality	Percentage				
		Sensitivity	Specificity	PPV	NPV	Accuracy
Overall	SSRS SPECT/CT	0.60	0.99	0.96	0.83	0.86
	<sup>68</sup> Ga-DOTATATE PET/CT	0.96	0.97	0.94	0.98	0.97
	WB DWI	0.72	1.00	1.00	0.88	0.91

#### Limitations

1. Very small population of patients who have suspected recurrence of NET
2. Patient level data not detailed
3. Changes in management due to DOTATATE scans mentioned briefly (not specified) related to detection of bone lesions
4. Comparator was MRI and Tc99m octreotide.

#### Recommendation

*The article supports the use of Ga68 PET as an adjunct to other diagnostic tests in this orphan population similar to other diagnostic agents that have been approved as noted in the recommendation for the article above.*

(b) (4)

#### Data Quality and Integrity – Reviewers’ Assessment

OSI inspection was not conducted for this literature review. There are no financial disclosure issues.

#### Efficacy Results – Secondary and other relevant endpoints

See discussion above.

#### Dose/Dose Response

Not applicable.

#### Durability of Response

Not applicable.

#### Persistence of Effect

Not applicable.

## 6.2. Use of 68Ga-DOTATATE PET scanning for diagnosis and treatment of metastatic neuroendocrine tumors – single center expanded access study

### 6.2.1. Study Design

#### Overview and Objective

The trial was initially designed as an expanded access protocol with a request to charge to make the product available to patients in the US without having to travel to Europe to obtain the PET scan. Therefore, the protocol was not designed to support drug development for marketing approval.

#### Trial Design

The study is a prospective, single center, open label protocol for NET patients with a previously obtained OctreoScan and conventional imaging. The images were read in a blinded fashion by two independent readers blinded to other information other than participation in the trial. Adjudication was performed as needed. The blinded reads were reviewed to stage the patient's extent of disease relative to the presence of tumor, resectability / extent of tumor, and intensity / presence of somatostatin receptor expression.

#### Scan interpretation:

The following comparisons were performed and reported:

- a) PET performance compared to standard of truth
- b) SPECT performance compared to standard of truth
- c) Performance results of 'a' compared to results of 'b'
- d) Agreement between PET performance and SPECT performance, without taking care of the standard of truth results

#### Performance:

The standard of truth (SOT) chosen and agreed to by the Division was standard of care anatomical conventional imaging with histopathology where available. The SOT here would be more properly termed SOR, i.e. Standard of Reference; "sensitivity" and "specificity" as measures of performance being measures of agreement with a respective SOR.

#### Patient management:

A board-certified oncology surgeon separately assessed the impact on care by comparing the intended treatment prior to and after the 68Ga-DOTATATE scan, on a per-patient basis. Initial treatment plan was elaborated using all available clinical, histopathology and imaging information, including 111In-pentetreotide scans. This initial treatment plan was then reviewed after adding the information from the 68Ga-DOTATATE scan. The definitions for change were:

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- Minor impact in treatment was characterized by a change within a treatment modality (“intramodality”), such as extent in surgery.
- Major impact on treatment was characterized by a change in treatment modality (“intermodality”). The addition of PRRT where previously not indicated, or cancellation of surgery due to evidence of greater extent of disease on 68Ga-DOTATATE scan, are examples of intermodality treatment changes.
- No specific details about the decision process were collected; only the conclusion of the scans and the impact on patient treatment management of adding 68Ga-DOATATE to the conventional diagnostic tools (including 111In-pentetreotide imaging) were recorded.

**Reviewer comment:**

*This protocol was submitted in 2011 as expanded access including a request to charge. The original intent of the investigator was to provide practice of medicine access to the drug for patients with NETs. The sponsor (AAA) subsequently entered into a relationship with VUMC for data sharing. Therefore, the data obtained from VUMC does not meet the rigor expected from a clinical trial. For example, the patient population was determined by referral of essentially any patient with an NET from the VUMC NET clinic (although this may be reflective of the eventual actual use of the product for this rare disease and population). Additionally, there was no formal statistical analysis plan a priori. The information on efficacy may be supportive to the literature review for disease localization or as an adjunct diagnostic procedure*

*Individual patient data on primary staging before surgery, prior curative primary resection, prior clinical recurrence, etc. were not collected and therefore are not available for sub-group analysis.*

*There are shortcomings related to the response about image interpretation. For example, the sponsor did not document or record the adjudication process nor did they provide detailed results of the blinded assessment. The reported assessment was binary (disease/no disease).*

*In discussions with the sponsor, the division previously agreed that the VUMC data could be considered contributory/supportive to the literature data. Furthermore, the division was aware that the VUMC data was originally designed as expanded access and knew that there could potentially be issues related to study design and conduct. The unique circumstances regarding*

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*this drug history and development program require regulatory discretion and latitude when interpreting results and assessing adequacy.*

### **Study Endpoints**

Demonstrate the safety and efficacy of 68Ga-DOTATATE.

Demonstrate impact on care that results from adding 68Ga-DOTATATE PET/CT to current standard of care imaging.

### **Statistical Analysis Plan**

There was no formal statistical analysis plan submitted.

### **Protocol Amendments**

Not applicable.

### **Data Quality and Integrity: Sponsor's Assurance**

#### **6.2.2. Study Results**

### **Compliance with Good Clinical Practices**

The study was conducted as an expanded access protocol for practice of medicine.

### **Financial Disclosure**

No conflicts.

### **Patient Disposition**

This information was not collected. The patients were scanned and returned to their private physician.

### **Protocol Violations/Deviations**

Patients who did not have an OctreoScan were not included in the efficacy endpoint but were included in safety endpoint.

### **Table of Demographic Characteristics**

Figure 6: Demographic information

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	<b>Safety Set</b>	<b>FAS</b>
	<b>N=97</b>	<b>N=78</b>
Gender Female n (%)	56 (58)	49 (63)
Mean Age (SD)	53.7 (11)	53.4 (11)
Primary tumor location n (%)		
Mid-gut carcinoid	44 (45)	37 (47)
Other gastroenteropancreatic	22 (23)	18 (23)
Hindgut or rectum	3 (3)	3 (4)
Pulmonary	7 (7)	5 (6)
Symptoms only	7 (7)	7 (9)
Other	2 (2)	1 (1)
Unknown primary	12 (12)	7 (9)

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Not collected.

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Not applicable.

**Efficacy Results - Primary Endpoint** – See diagram below from submission

97 patients total received a dose of investigational product

19 patients excluded

- 10: Lack of SPECT scan available
- 4: Time interval between PET and SPECT > 3 years
- 5: SPECT pre-op and PET post-op

78 patients with SPECT and PET scans available for review

61/78 scans agreed (disease vs. no disease, as determined by the SOR)

- 36 disease
- 25 no disease

17/78 scans did not agree (disease vs. no disease, as determined by the SOR)

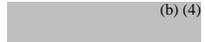
- 14 disease
- 3 no disease
- In this setting, the PET localized 12 extra cancer cases (FN In-111) and excluded 1 cancer case (FP In-111).

“Sensitivity” of 68Ga-DOTATATE 96.0% (95% CI: [86.3%; 99.5%])

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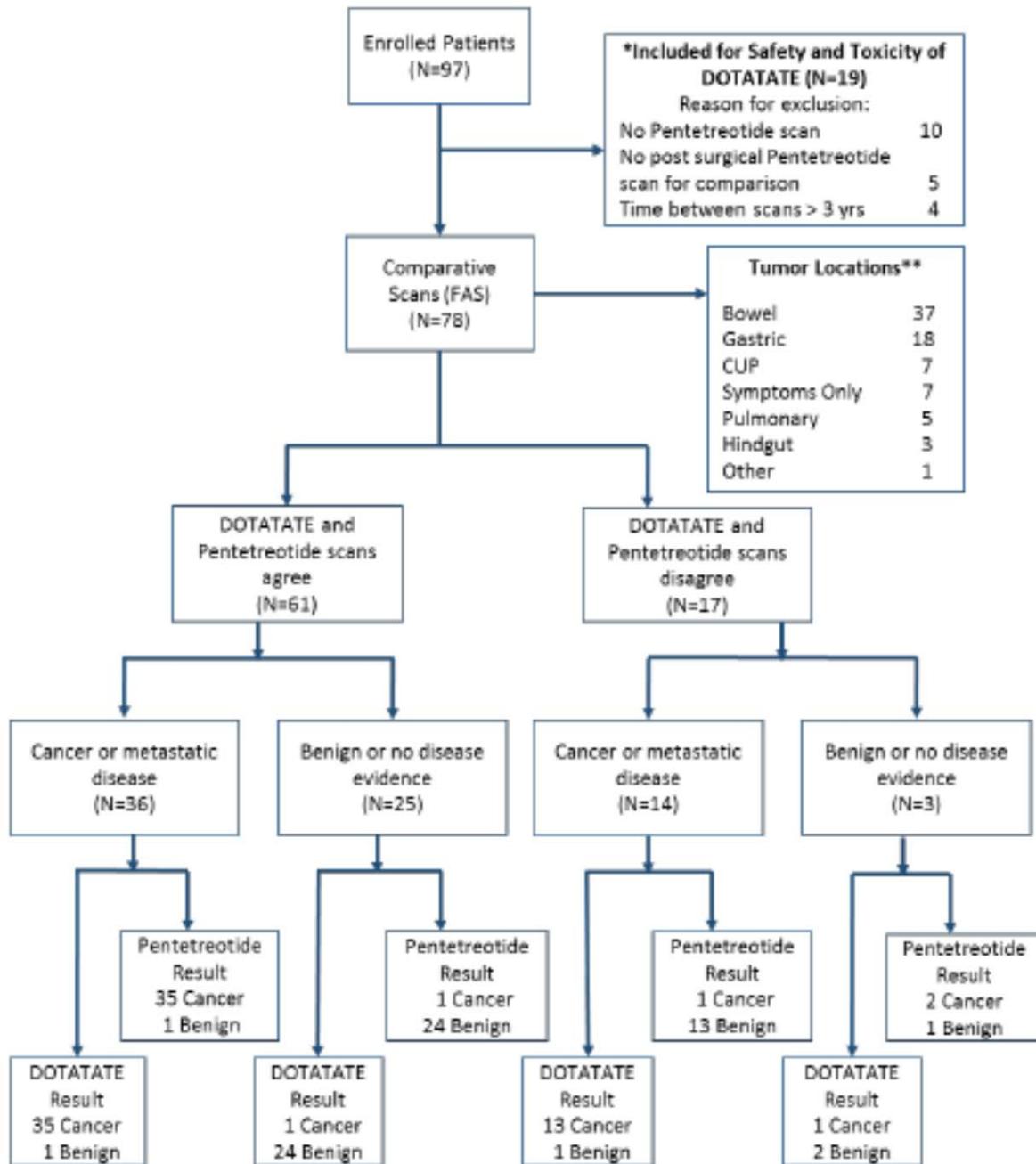
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“Sensitivity” of 111In-pentetreotide 72.0% (95% CI: [57.5%; 83.8%])

“Specificities” were similar 92.9% and 89.3% respectively, with overlapping confidence intervals.

In related calculations, 68Ga-DOTATATE showed a higher “negative predictive value”, whereas “positive predictive values” of both products were similar.

Figure 7: VUMC Results



**Limitations of the study**

1. The study was not designed to be a clinical trial for drug development.
2. The time interval between PET and SPECT varied.
3. The patients had the SPECT scan performed at an outside institution (typically) and leading to variability in the technology (planar vs. SPECT vs. SPECT/CT).
4. The patient population was variable and dependent upon referral.

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**Reviewer comment:**

The sponsor has suggested the following indication statement:

(b) (4)

OctreoScan (comparator) labeled indication statement:

“Indium In-111 pentetate is an agent for the scintigraphic **localization** of primary and metastatic neuroendocrine tumors bearing somatostatin receptors.”

Review of the literature and the VUMC supplementary data

(b) (4)

. I would be in favor of a localization indication similar to the comparator product, OctreoScan (above), or a general indication statement such as “an adjunct to other diagnostic tests” (similar to that given to AdreView as shown below) as the Ga68 PET scan was found to add information to the standard of care anatomical imaging and clinical information.

AdreView label:

“use in the detection of primary or metastatic pheochromocytoma or neuroblastoma **as an adjunct to other diagnostic tests**”

Note from the July 2014 meeting with the sponsor, the division had stated that if the literature review and the VUMC data were found to be insufficient that the sponsor would need to conduct a clinical trial. As the information/data has been reviewed, it is this reviewer’s opinion that the information submitted is insufficient to justify their requested indication statement. Given the totality of the data, circumstances regarding the complicated regulatory history of this class of products, and the rare nature of the disease, it is reasonable to exercise regulatory discretion and to offer the sponsor an indication as I have noted in the paragraphs above.

**Data Quality and Integrity - Reviewers' Assessment**

OSI was asked to visit the site to confirm data. At the time of this review, the OSI report was not available.

**Efficacy Results - Secondary and other relevant endpoints**

When assessing the impact on patient management, specific details were not detailed or provided. The response was categorical only. However, the according to the sponsor those cases excluded patients as surgical candidates (N=12).

~ 1/3rd of patients had some change in their management based upon the PET.

2 FP PET

2 FP In-111 (but TN PET)

1 double FN (other diagnostic tools provided confirmation of the disease)

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Sponsor states: “no case of 68Ga-DOTATATE imaging was clinically inferior to 111In-pentetreotide imaging. Correct clinical management could be made in all patients with imaging limited to 68Ga-DOTATATE plus diagnostic CT and/or contrast-enhanced MRI.”

An IR was sent to the sponsor 11/17/15 asking for detailed information on the 17 patients in which the PET and SPECT were discordant. To date, that information has not been received. It will be reviewed when it arrives and if there is a significant finding pertinent to approval an addendum will be filed to this review.

### **Dose/Dose Response**

Not applicable.

### **Durability of Response**

Not applicable.

### **Persistence of Effect**

Not applicable.

### **Additional Analyses Conducted on the Individual Trial**

Not applicable.

## **7 Integrated Review of Effectiveness**

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### **7.1. Assessment of Efficacy Across Trials**

#### **7.1.1. Primary Endpoints**

Not applicable.

#### **7.1.2. Secondary and Other Endpoints**

Not applicable.

#### **7.1.3. Subpopulations**

Figure 8 below reproduced and modified from Navalkele et al shows the frequency and incidence rates for malignant neuroendocrine tumors and neuroblastoma by age, stage, and grade, 0–29 years, 9 Standard SEER Registries, 1975–2006.

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Stage **	Localized	508	1.3	215	0.6
	Regional	233	0.6	337	1.0
	Distant	113	0.3	840	2.5
	Unstaged	100	0.3	257	0.8
	Blank ***	118	0.3	15	0.0
Grade	Well differentiated	54	0.1	43	0.1
	Moderately differentiated	23	0.0	22	0.1
	Poorly differentiated	91	0.2	254	0.7
	Undifferentiated	67	0.2	166	0.5
	Unknown	838	2.2	1,179	3.5

There is very limited information available regarding the use of this product in the pediatric population. Below is a summary of 1 retrospective article that administered the product to the NET pediatric population for identification of bone metastases followed by 2 articles found by the reviewer that utilized the product to select patients for therapeutic intervention in the pediatric neuroblastoma population.

**Goel, R et al, 2014.** Ga68 DOTATATE positron emission tomography/computed tomography scan in the detection of bone metastases in pediatric neuroendocrine tumors. *Indian Journal of Nuclear Medicine* 29. doi: 10.4103/09723919.125762.

Investigational agent: Ga68 DOTATATE

Comparator agent: CT scan

Purpose: primary staging

N = 30 patients ages 1-18 years; 18 males and 12 females with histologically confirmed 5 GEP-NETs, 11 neuroblastomas and 8 pheochromocytomas, 2 pancreatic NETs, 2 paragangliomas, 1 bronchial carcinoid, and 1 ganglioneuroma.

Dose: 18-74 MBq IV (*The author did not state how this dose was determined. However, this dose is consistent with the dose used in other articles for adults (2 MBq/kg) and with the dose used in the VUMC trial if one considers that a 1 year old weighs ~20 pounds*)

Endpoint: bone metastases detection per patient and per lesion basis

Image reads: not specified

Results

- 17/30 no bone metastases on any imaging or follow up
- 13/30 + bone metastases
  - 13/13 + PET detecting 225 lesions
  - 9/13 + CT detecting 84 lesions
  - Lesion sensitivity and specificity were not calculated due to

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lack of histopathological correlation

- 3/30 + PET were upstaged to stage IV due to bone metastases; management change implied but details not stated
- 27/30 PET + primary site (not planned as part of the review)
- 3/30 PET (-) primary site (1 pheo; 2 GEP NET)
- Toxicity was not mentioned

*Reviewer comment: The article may be considered supportive of the use of the product in the pediatric population at ~ the same dosing calculation as adults. Toxicity was not mentioned. There were patients who had (-) PET and no mention of false positive results. The primary site was identified in 27/30 patients.*

**Gains et al, 2011.** 177Lu DOTATATE molecular radiotherapy for childhood neuroblastoma. *Journal of Nuclear Medicine*; 52:1041–1047. DOI: 10.2967/jnumed.110.085100.

8 children scanned (ages 2-14 years old)

Dose: at least 100 MBq

No safety issues discussed related to PET.

Study was designed to assess use of Lu177 dotatate.

**Kong et al, 2015.** Initial Experience With Gallium-68 DOTA-Octreotate PET/CT and Peptide Receptor Radionuclide Therapy for Pediatric Patients With Refractory Metastatic Neuroblastoma. *Journal of Pediatric Hematology Oncology* published online early no citation available.

Note that this article was about the use of the DOTATATE as a therapeutic. The primary focus of the article was not to discuss the diagnostic agent.

8 patients (2-9 years old) with residual neuroblastoma (heavily pretreated)

8 baseline studies retrospectively reviewed and compared to MIBG scintigraphy

2.6 MBq/kg (*Note: This is slightly larger than that proposed by the sponsor*)

Blinded reads by 2 readers

No safety issues mentioned

Results: GaTATE PET/CT demonstrated additional sites of disease in 3 of the 8 studies (38%).

One was upstaged by identification of unexpected marrow involvement, confirmed on bone marrow biopsy.

*Reviewer comment: These 3 articles do not report any safety issues related to the use of Ga68*

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*DOTATATE in the pediatric population at doses that are consistent with that proposed by the sponsor.*

#### **7.1.4. Dose and Dose-Response**

Not applicable.

#### **7.1.5. Onset, Duration, and Durability of Efficacy Effects**

There is no therapeutic treatment effect. This product is a single use, diagnostic agent with a 68 minute half-life sufficient for obtaining interpretable images. There is no expectation of durability or clinical benefit beyond the time limit of the radioisotope.

### **7.2. Additional Efficacy Considerations**

#### **7.2.1. Considerations on Benefit in the Postmarket Setting**

The reviewer does not recommend any postmarketing requirements. Based upon review of the literature and the patient population studied in the VUMC expanded access trial, the patient population in the postmarketing setting is expected to be similar.

#### **7.2.2. Other Relevant Benefits**

The benefits of this product are:

- Does not require an on-site cyclotron
- Has a shorter half-life (68 minutes) than the approved product (67 hours)
- Has a shorter imaging window (2 hours) than the approved product (2 days)
- The radiation absorbed dose to the patient is less than that of the approved product (~4 mSv vs. ~26 mSv)
- The difference in technology of PET vs. SPECT provides for greater image resolution

The characteristics of the PET product noted above provide for improved patient safety (less radiation dose) as well as improved scheduling for the clinic and the patient as it requires less imaging time and fewer appointments to obtain those images.

### **7.3. Integrated Assessment of Effectiveness**

In this rare patient population, the product under review is at least as effective with respect to

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sensitivity and specificity as the approved product. Based upon the review of the literature and the VUMC clinical data the benefit of this product is demonstrated by the ability to be produced on site rather than requiring a cyclotron, decreased radiation dose to the patient, improved patient image scheduling and convenience, and improved image resolution. The increased image resolution most likely due to the technological characteristics of PET vs. SPECT enables the scan to capture clearer images and smaller lesions probably accounting for the equal to better sensitivity. Unfortunately, the development program did not include prospective and randomized trials with blinded image interpretation and blinded patient management determinations with and without the PET scan. Even the VUMC trial did not provide sufficiently detailed methodology (b) (4). The information is adequate to allow for a localization claim or as an adjunct to other diagnostic tests which in this case would be anatomical imaging and laboratory tests.

## 8 Review of Safety

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There are no safety issues associated with this development program.

### 8.1. Safety Review Approach

There are no safety issues.

### 8.2. Review of the Safety Database

#### 8.2.1. Overall Exposure

This product is a single administration product. It is possible that patients may receive future single administrations over the course of their disease at times of recurrence or response to therapy. The VUMC expanded access protocol included 97 patients. The number of patients reported in the literature is difficult to specify given the possibility that some patients may be counted in >1 article. It is conceivable that >1400 patients have received this product.

#### 8.2.2. Relevant characteristics of the safety population:

The safety database consisted of the spectrum of patients one would find in the indicated population.

#### 8.2.3. Adequacy of the safety database:

The size and adequacy of the safety database for this rare disease, single administration

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product that contains a sub-pharmacologic mass dose is adequate.

### **8.3. Adequacy of Applicant's Clinical Safety Assessments**

#### **8.3.1. Issues Regarding Data Integrity and Submission Quality**

Not applicable. The sponsor submitted summary tabular tables.

#### **8.3.2. Categorization of Adverse Events**

There is minimal information regarding adverse events related to this product in the literature.

#### **8.3.3. Routine Clinical Tests**

The VUMC expanded access protocol collected baseline assessments and some laboratory tests before and after the PET scan when available. The sponsor utilized the NCI CTCAE scale.

### **8.4. Safety Results**

#### **8.4.1. Deaths**

There were no deaths.

#### **8.4.2. Serious Adverse Events**

There were no SAEs.

#### **8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects**

There were no drops outs or discontinuations due to an AE of the drug. There were no protocol specified criteria for withdrawal of patients as this is a single administration trial.

#### **8.4.4. Significant Adverse Events**

There were no significant AEs.

#### **8.4.5. Treatment Emergent Adverse Events and Adverse Reactions**

There are no specific TEAEs to discuss.

#### **8.4.6. Laboratory Findings**

There were no occurrences of unscheduled visits or laboratory tests obtained.

The sponsor submitted the following possibly related to study intervention:

- Two patients had elevated glucose. Both patients were on long-acting somatostatin analog medication, known to cause glucose intolerance in up to 25% of patients. One of these two patients is also a diabetic. In addition, post-scan fasting glucose plasma levels could not be consistently obtained after the participants returned home, so these values may not have been fasting.
- One patient with elevation in liver function tests had known extensive liver metastases.

While the sponsor states that the findings may be possibly related to the drug it is unlikely given the sub-pharmacologic mass dose of the drug and the small numbers.

#### 8.4.7. Vital Signs

The data submitted from VUMC:

One patient with a baseline heart rate of 87 had post-scan tachycardia of 112, asymptomatic, spontaneously returning to <100 beats per minute within an hour.

One patient had an unexplained drop in post-scan oxygen saturation on room air (pre-injection 98%, post scan 90%), spontaneously resolving.

One patient had minor itching the day after the 68Ga-DOTATATE injection at the injection site, spontaneously resolving.

#### 8.4.8. Electrocardiograms (ECGs)

ECGs were collected in a small subset of subjects in the VUMC trial pre and post administration of the product. No changes were reported by the sponsor. The sponsor did not specify the interpretation method.

#### 8.4.9. QT

No QT clinical trials were conducted.

#### 8.4.10. Immunogenicity

Not applicable.

### 8.5. Analysis of Submission-Specific Safety Issues

There were no safety issues identified.

### 8.6. Specific Safety Studies/Clinical Trials

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There were no specific studies or clinical trials conducted to evaluate a special safety concern.

## **8.7. Additional Safety Explorations**

### **8.7.1. Human Carcinogenicity or Tumor Development**

There were no human tumors reported during drug development. There were no deaths, serious AEs, or discontinuations due to AE.

### **8.7.2. Human Reproduction and Pregnancy**

There were no pregnancies or drug exposure to lactating women during the development program.

### **8.7.3. Pediatrics and Assessment of Effects on Growth**

The sponsor has orphan designation and is exempt from pediatric studies.

### **8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

There is no overdose experience with this product. There are no issues related to drug abuse potential, withdrawal, or rebound.

## **8.8. Safety in the Postmarket Setting**

### **8.8.1. Safety Concerns Identified Through Postmarket Experience**

There is no postmarketing experience.

### **8.8.2. Expectations on Safety in the Postmarket Setting**

There are no anticipated safety concerns.

## **8.9. Additional Safety Issues From Other Disciplines**

None.

## **8.10. Integrated Assessment of Safety**

There are no safety concerns specific to this diagnostic PET radiopharmaceutical class product.

# **9 Advisory Committee Meeting and Other External Consultations**

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An AC meeting was not held. There was no interaction with consultants, special government employees, or patient stakeholders.

A regulatory briefing is planned for 1/22/16 (after submission of this review).

## **10 Labeling Recommendations**

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### **10.1. Prescribing Information**

The label review is ongoing and is not complete at the time of this review. The main issue in this reviewer's opinion related to the label is the indication statement. The sponsor is seeking a

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It is my opinion that the level of evidence required for this indication has not been achieved. Based upon the information submitted it is my suggestion that the indication be limited to either "localization" similar to the approved SPECT product or to "as an adjunct to other diagnostic tests" similar to AdreView.

### **10.2. Patient Labeling**

There is no need for a Medication Guide, patient package insert, or instructions for use to be developed. This product is not marketed to the general population nor is it administered by the patient. Its use and administration are restricted to those physicians and health care providers who have the appropriate radiation training and in accordance with NRC regulations.

### **10.3. Nonprescription Labeling**

Not applicable.

## **11 Risk Evaluation and Mitigation Strategies (REMS)**

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Given the favorable safety profile of this drug, no additional risk management strategies are required beyond the recommended labeling. Therefore, the subsequent subsections are not applicable for this review.

### **11.1. Safety Issue(s) that Warrant Consideration of a REMS**

Not applicable.

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### 11.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

### 11.3. Recommendations on REMS

Not applicable.

## 12 Postmarketing Requirements and Commitments

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There are no PMRs. The product has Orphan designation and is exempt from pediatric studies.

## 13 Appendices

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### 13.1. References

Etchebere, E. C., de Oliveira Santos, A., Gumz, B., Vicente, A., Hoff, P. G., Corradi, G., Ichiki, W. A., de Almeida Filho, J. G., Cantoni, S., Camargo, E. E. and Costa, F. P. (2014). 68Ga-DOTATATE PET/CT, 99mTc-HYNIC-octreotide SPECT/CT, and whole-body MR imaging in detection of neuroendocrine tumors: a prospective trial. *J Nucl Med* 55(10), 1598-1604.

Garcia-Carbonero et al, 2014. SEOM clinical guidelines for the diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) 2014. *Clin Transl Oncol* 16:1025–1034. DOI 10.1007/s12094-014-1214-6.

Goel, R., Shukla, J., Bansal, D., Sodhi, K., Bhattacharya, A., Marwaha, R. K. and Mittal, B. R. (2014). (68)Ga-DOTATATE positron emission tomography/computed tomography scan in the detection of bone metastases in pediatric neuroendocrine tumors. *Indian J Nucl Med* 29(1), 13-17.

Hofman, M. S., Kong, G., Neels, O. C., Eu, P., Hong, E. and Hicks, R. J. (2012). High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. *Journal of medical imaging and radiation oncology* 56(1), 40-47.

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Srirajaskanthan, R., Kayani, I., Quigley, A. M., Soh, J., Caplin, M. E. and Bomanji, J. (2010). The role of 68Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on 111In-DTPA-octreotide scintigraphy. *J Nucl Med* 51(6), 875-882.

Wild, D., Bomanji, J. B., Benkert, P., Maecke, H., Ell, P. J., Reubi, J. C. and Caplin, M. E. (2013). Comparison of 68Ga-DOTANOC and 68Ga-DOTATATE PET/CT within patients with gastroenteropancreatic neuroendocrine tumors. *J Nucl Med* 54(3), 364-372.

### 13.2. Financial Disclosure

There are no disclosable financial interests for the VUMC clinical study.

**Covered Clinical Study:** Use of 68Ga-DOTATATE PET scanning for diagnosis and treatment of metastatic neuroendocrine tumors (conducted at VUMC)

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>6</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>n/a</u>  Significant payments of other sorts: <u>n/a</u>  Proprietary interest in the product tested held by investigator: <u>n/a</u>		

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Significant equity interest held by investigator: n/a		
Sponsor of covered study: <u>n/a</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CYNTHIA A WELSH  
12/04/2015

ALEXANDER GOROVETS  
12/04/2015