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RESEARCH**

APPLICATION NUMBER:

210828Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NME & 505 (b)(2)
Application Number(s)	NDA 210828
Priority or Standard	Standard
Submit Date(s)	May 23, 2018
Received Date(s)	May 23, 2018
PDUFA Goal Date	August 23, 2019
Division/Office	Office of Drug Evaluation IV/Division of Medical Imaging Products (DMIP/ODEIV)
Review Completion Date	TBD
Established/Proper Name	Ga-68-DOTATOC injection
(Proposed) Trade Name	Not applicable
Pharmacologic Class	Radioactive diagnostic agent
Code name	IC2000
Applicant	University of Iowa Health Care/P.E.T. Imaging Center
Dosage Form	Injection: Clear, colorless solution containing 18.5 to 148 MBq/mL (0.5 to 4 mCi/mL) of Ga-68-DOTATOC injection at end of synthesis (EOS) (approximately 14 mL volume) in a 30 mL multiple-dose vial.
Applicant proposed Dosing Regimen	For adults: 148 MBq (4 mCi); for pediatric patients: 1.59 MBq/kg (0.043 mCi/kg) with a range of 11.1 MBq (0.3 mCi) to 111 MBq (3 mCi)
Applicant Proposed Indication(s)/Population(s)	For localization of somatostatin receptor positive neuroendocrine tumors (NETs) (b) (4) in adult and pediatric (b) (4) patients.
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	Indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) (b) (4) in adult and pediatric (b) (4) patients.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	55937004
Recommended Dosing Regimen	Adults: Flat dose of 4 mCi. Pediatric patients: 0.043 mCi/kg with a range of 0.3 to 3 mCi.

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Diane Hanner
Nonclinical Reviewer	Ronald Honchel
Nonclinical Team Leader	Adebayo A. Laniyonu
Office of Clinical Pharmacology Reviewer	Sam Habet
Office of Clinical Pharmacology Team Leader	Christy John
Clinical Reviewer	Phillip Davis, Qi Feng
Clinical Team Leader	Nushin Todd, Anthony Fotenos
Statistical Primary Reviewer	Xiangmin Zhang
Statistical Secondary Review	Jyoti Zalkikar
Cross-Disciplinary Team Leader	Nushin Todd
Division Deputy Director (DMIP)	N/A
Division Director (DMIP)	Libero Marzella
Deputy Division Director (Acting, OB/DB1)	Sue-Jane Wang
Office Director (or designated signatory authority)	Charles Ganley

Additional Reviewers of Application

OPQ	John Amartey
Microbiology	Alifiya Gahadiali
OPDP	David Foss
OSI	Not applicable
OSE/DEPI	Carolyn McCloskey
OSE/DMEPA	Idalia Rychlik Hina Mehta
OSE/DRISK	Brad Moriyama Liz Everhart
Other	Steven Bird Martin Pollock Neha Gada (DPV)

OPQ = Office of Pharmaceutical Quality

OPDP = Office of Prescription Drug Promotion

OSI = Office of Scientific Investigations

OSE = Office of Surveillance and Epidemiology

DEPI = Division of Epidemiology

DMEPA = Division of Medication Error Prevention and Analysis

DRISK = Division of Risk Management

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Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Ronald Honchel, PhD	ODE4/DMIP	Sections: 5 (Nonclinical)	Select one: X Authored ___ Approved
	Signature:			
Nonclinical Supervisor	Adebayo A. Laniyonu, PhD	ODE4/DMIP	Sections: 5 (Nonclinical)	Select one: ___ Authored X Approved
	Signature:			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Sam Habet PhD	OCP/DCP5	Section:	Select one: X Authored ___ Approved
	Signature:			
Clinical Pharmacology Team Leader	John Christy, Ph D	OCP/DCP5	Section:	Select one: ___ Authored X Approved
	Signature:			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Qi Feng, MD	ODE4/DMIP	Sections: 2,3,7,8, Labeling	Select one: x Authored ___ Approved
	Signature:			
Clinical Team Leader	Anthony Fotenos, MD, PhD	ODE4/DMIP	Sections: 2,3,7,8, Labeling	Select one: ___ Authored X Approved
	Signature:			
Clinical team leader/CDTL	Nushin Todd, MD, PhD	ODE4/DMIP	Sections: All Sections	Select one: ___ Authored X Approved
	Signature:			
Associate Director of Labeling	Michele Fedowitz, MD,	ODE4/DMIP	Sections: 10; Labeling	Select one: X Authored ___ Approved
Deputy Division Director (Clinical)	N/A	ODE4/DMIP	Sections: All Sections	Select one: ___ Authored X Approved
Statistical Primary Reviewer	Xiangmin Zhang, PhD	OB/DB1	Sections:8 Stats, Clin, Evaluations	Select one: X Authored ___ Approved
	Signature:			
Statistical Secondary Reviewer	Jyoti Zalkikar, PhD	OB/DB1	Sections: 8 Stats, Clin, Evaluations	Select one: X Authored ___ Approved
Deputy Division Director (Acting, Statistical)	Sue Jane Wang, PhD	OB/DB1	Sections:8 Stats, Clin, Evaluations	Select one: ___ Authored X Approved
	Signature:			

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Division Director	Louis Marzella, MD, PhD	ODE4/DMIP	Sections: All Sections	Select one: ____ Authored X Approved
	Signature:			
Director	Charles Ganley, MD	ODEIV	Sections: All Sections	Select one: ____ Authored X Approved

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Clinical Team Leader
DHOT	Division of Hematology Oncology Toxicology
ECG	electrocardiogram
FDA	Food and Drug Administration
GEP	gastroenteropancreatic
IND	Investigational New Drug
MBq	megabecquerel
mCi	millicurie
MR	magnetic resonance
mSv	millisievert
NEN	neuroendocrine neoplasms
NET	neuroendocrine tumor
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PET	positron emission tomography
PI	prescribing information/principal investigator
PK	pharmacokinetics
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SNET	suspected neuroendocrine tumor
SPECT	single-photon emission computerized tomography
SSTR	somatostatin receptor
SUV _{max}	standard uptake value maximum

1. Executive Summary

1.1. Product Introduction

NDA 210828 for Gallium Ga 68 DOTA-TOC (Ga-68-DOTATOC) injection is a 505(b)(2) application with proposed indication for use with positron emission tomography (PET) for localization of somatostatin receptor (SSTR) positive neuroendocrine tumors (NETs). The drug substance is manufactured from two materials, a radio-isotope Ga-68 and GMP grade DOTATOC via a (b) (4) Ga-68-DOTATOC binds to SSTRs, with highest affinity for subtype 2 receptors (SSTR2). It binds to cells that express SSTRs including certain malignant cells, which commonly overexpress SSTR2 receptors. Ga-68 is a β^+ emitting radionuclide with associated 511 keV annihilation photons that allow PET imaging. Ga-68-DOTATOC distributes to all SSTR2-expressing organs such as normal pituitary, thyroid, spleen, adrenals, kidney, pancreas, prostate, liver, and salivary glands.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The clinical review team recommends approval. The approval for this NDA is based upon the totality of the data submitted, which included a retrospective analysis of three prospective clinical trials (RET-NET-001) and a meta-analysis of the clinical literature to support the safe and effective use of Ga-68-DOTATOC for the indication sought. For the localization of SSTR positive NETs with PET, the Applicant's clinical trial data demonstrated acceptable positive and negative percent agreements of the drug for detection of NETs. There were no deaths, serious adverse events (SAE), or other significant adverse events (AEs) reported during any of the three prospective clinical studies. There were no individual AEs reported at a rate of greater than or equal to 3% among the total 334 patients exposed to the drug.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The clinical studies (RET-NET-01) and a meta-analysis of the published literature conducted by the Applicant demonstrate that Ga-68-DOTATOC is an effective imaging agent for the detection of somatostatin receptor (SSTR)-positive neuroendocrine tumor (NET) disease by positron emission tomography (PET) imaging for adult and pediatric patients. The overall safety profile of Ga-68-DOTATOC is favorable.

Table 1. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Neuroendocrine tumors (NETs) are a heterogeneous group of rare tumors that arise from neuroendocrine cells found throughout the body. The clinical behavior of NETs is very variable, with each anatomic site having distinct clinical-pathologic features. These features include morphology, expression of neuroendocrine markers, and clinical syndromes caused by secretion of hormones and other biologically active substances. Most NETs are slow-growing, tumor grading is an important determinant of prognosis. In about 20% of cases NETs are metastatic at the time of diagnosis. The annual incidence of NETs is 2.5 to 5 per 100,000.	Identification and histological characterization of NETs is important for clinical management
Current Treatment Options	NETs are challenging to diagnose. Tumor marker assays are used for diagnosis and are valuable for prognosis. Standard anatomical imaging approaches are used for tumor localization and for assessment of response to treatment. These procedures include radiography, angiography, computed tomography, magnetic resonance imaging, ultrasonography. Radiopharmaceutical-based molecular imaging is an important diagnostic modality. Pharmacophores in current use (diethylenetriaminopentaacetic (DTPA))	Radiopharmaceuticals that target somatostatin receptors (SSTR2) are established as an important diagnostic option and therapeutic option for patients with NETs. PET imaging using positron emitting radionuclides (e.g. Ga-68) provides good resolution and is in use for diagnosis and patient selection for PPRT. Ga-68-

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	conjugate of octreotide (pentetreotide) and DOTA conjugate of octreotate (DOTATATE)) target somatostatin receptors overexpressed on differentiated NETs. The signaling radionuclides are either gamma emitters (I-111, used for planar or SPECT imaging), or positron emitters (Ga-68, used for PET imaging). For clinical management surgical resection of primary NETs may be curative, surgery has also a role for debulking. Systemic anti-tumor therapies include peptide receptor radionuclide therapy (PPRT) using beta radiation emitting radionuclides (Lu-177 bound to DOTATATE).	DOTATOC provides another imaging option to the two marketed products.
Benefit	The primary data source for the efficacy and safety of Ga-68-DOTATOC was study RET-NET-01, a retrospective analysis of data from three prospective studies conducted at the University of Iowa. The efficacy population consisted of all patients who participated in one of the three prospective studies, received a Ga-68-DOTATOC scan, and had sufficient data to establish NET status based on a composite reference standard. The study met its positive- and negative-percent agreement thresholds based on blinded consensus reads. A meta-analysis based on a systematic review of the scientific literature provided supportive evidence of diagnostic efficacy.	The long-term clinical experience with the use of somatostatin analogues for diagnostic and therapeutic purposes provides strong rationale for the use of Ga-68-DOTATOC in patients with NETs. The biodistribution of the target receptor (SSR2) and the interaction of SSR2 with the pharmacophore are well understood and are not dependent on age, gender, and disease stages. The radionuclide moiety (Ga 68) binding to DOTA and its imaging performance are also well understood. The scientific literature provides ample supportive evidence of diagnostic performance across multiple centers.
Risk and Risk management	No deaths or other serious adverse events were reported among the 334 patients in the clinical study. The total effective radiation absorbed doses was 3 mSv.	Ga-68-DOTATOC is a radiopharmaceutical administered as a single dose with a mass-dose up to (b) (4) micrograms; a micro-dose that precludes

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Dimension	Evidence and Uncertainties	Conclusions ad Reasons
		pharmacologic activity. These dose levels account for a very benign safety profile. The radioactivity dose (4 mCi) is acceptable. No risk management steps are required.

Abbreviations: DOTA = tetraxetan; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

1.4. Patient Experience Data

Table 2. Patient Experience Data Relevant to This Application

☐	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
	☐ Clinical outcome assessment (COA) data, such as	
	☐ Patient reported outcome (PRO)	
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
	☐ Input informed from participation in meetings with patient stakeholders	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Other: (Please specify):	
☒	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

The neuroendocrine system functions as a chemical messaging system and is comprised of neuroendocrine cells distributed throughout the body. Neuroendocrine cells share certain characteristics with cells in the nervous system and are found mainly throughout the gastrointestinal tract, respiratory system and thyroid. Neuroendocrine cells make up the neurohypophysis, parathyroid gland, and inner layer of the adrenal gland. The prostate, kidneys, cervix, ovaries, testicles, skin, thymus and liver all contain neuroendocrine cells.

Neuroendocrine neoplasms (NENs) are heterogeneous tumors with a common phenotype. There are two fundamentally different groups of NENs: well-differentiated, low-proliferating NENs, called neuroendocrine tumors (NETs) or carcinoids; and poorly differentiated, highly proliferating NENs, called small- or large-cell neuroendocrine carcinomas (NECs). Most (approximately 70%) NENs arise from the gut between stomach and rectum and pancreas (gastroenteropancreatic or GEP-NENs). The current World Health Organization classification of GEP-NENs uses the Ki-67 proliferation index and mitotic index for grading (see Table 3). Somatostatin receptors are overexpressed in NENs and can be targets for imaging and therapy.

Table 3. World Health Organization Classification 2017 for Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs)

Classification	Ki-67 index	Mitotic index
Well-differentiated NENs		
Neuroendocrine tumor (NET) G1	< 3%	< 2/10 HPF*
Neuroendocrine tumor (NET) G2	3 – 20%	2 – 20/10 HPF
Neuroendocrine tumor (NET) G3	> 20%	> 20/10 HPF
Poorly differentiated NENs		
Neuroendocrine carcinoma (NEC) G3	> 20%	> 20/10 HPF

*high-power fields

Source: (Ito et al. 2017)

2.2. Analysis of Current Treatment Options

Diagnostic imaging options for patients with known or suspected NENs consist of anatomical (computed tomography (CT), magnetic resonance imaging (MRI), ultrasound) and/or functional imaging with Octreoscan (In-111 pentetreotide) SPECT or Netspot (68Ga-DOTATATE) PET. In patients with NEC, fludeoxyglucose (FDG) F 18 PET may also be performed due to the high metabolic rate of poorly differentiated neoplasms and loss of SSTR positivity.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Table 4 summarizes the regulatory history and provides additional clinical context for Octreoscan and Netspot.

Table 4. Summary of Relevant Products to Ga-68-DOTATOC

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(Ga-68-DOTATOC)

Product Name	Octreoscan (Indium In 111 Pentetreotide)	Netspot (Gallium 68Ga-DOTATATE)
Approval date	6/2/1994	6/1/2016
Mechanism	Binds to somatostatin receptors	Binds to somatostatin receptors
Indication	Localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors	Localization of somatostatin receptor positive NETs in adult and pediatric patients
Isotope	Indium-111 (In-111)	Gallium-68 (Ga-68)
Decay by	Electron capture	Positron-emission
Decay half-life	67.3 h	68 min
Image acquisition	4 and 24 h or 24 and 48 h after injection	40 to 90 min after injection
Imaging	Planar and SPECT	PET
Radiation exposure (mSv)	13 for planar 26.1 for SPECT	3.2
Dosing/administration	Recommended intravenous dose for planar imaging is 111 MBq (3.0 mCi). Recommended intravenous dose for SPECT imaging is 222 MBq (6.0 mCi)	Recommended dose is 2 MBq/kg of body weight (0.054 mCi/kg) up to 200 MBq (5.4 mCi) administered as intravenous injection.
Efficacy information	Octreoscan was studied in nine unblinded clinical studies with a total of 309 evaluable patients. Octreoscan results were consistent with the final diagnosis (success) in 267 of 309 evaluable patients (86.4%).	Among 78 patients in whom CT and/or MR images and Octreoscan images were available, 68Ga-DOTATATE PET agreed with the CT and/or MR images in 74 patients.
Safety and tolerability issues	The following adverse events were observed in clinical trials at a frequency of less than 1% of 538 patients: dizziness, fever, flush, headache, hypotension, changes in liver enzymes, joint pain, nausea, sweating, and weakness.	No serious adverse reactions identified in three clinical studies and in a survey of the scientific literature.

Abbreviations: CT = computed tomography, h = hour, MBq = megabecquerel, mCi = millicurie, MR = magnetic resonance, mSv = millisievert, NET = neuroendocrine tumor, PET = positron emission tomography, SPECT = single-photon emission computed tomography

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant, University of Iowa Hospitals and Clinics (UIHC)-PET Imaging Center, developed Ga-68-DOTATOC with two investigational new drug (IND) applications, IND 114398 and IND 125673, which were initiated on February 10, 2012 and February 11, 2015, respectively.

- April 30, 2015: Meeting with FDA to review published data and data generated from two studies by Applicant.
- May 22, 2017: Applicant communicated with FDA on data and statistical analysis plan (SAP) submission.
- October 3, 2017: Pre-NDA meeting to discuss the content and format of the planned 505(b)(2) NDA submission.
- October 10, 2017: Pre-NDA CMC (chemistry, manufacturing, and controls) meeting to discuss the content and format of the planned 505(b)(2) NDA submission.
- May 23, 2018: Original NDA submitted.

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

4.1. Office of Scientific Investigations

An OSI inspection was not requested as the RET-NET study was a retrospective analysis and there were no major concerns regarding the integrity of the data. The patients were identified after they had received the study drug and images had been already acquired and used in the RET-NET study. Since the retrospective study did not involve the administration of any treatment, the information regarding clinical study management was not available.

4.2. Product Quality

Ga-68-DOTATOC injection is a sterile radiolabeled peptide (edotreotide) classified as a diagnostic radiopharmaceutical. The drug substance is the same as the drug product. The drug substance is (b) (4) from the drug substance precursor DOTATOC (b) (4). The Applicant utilizes (b) (4), to

manufacture the drug product. [REDACTED]

(b) (4)

[REDACTED] The DOTATOC is manufactured and supplied under current good manufacturing practice conditions. Product quality issues identified in the original submission were addressed through a series of information requests.

The Applicant submitted a comparability protocol [REDACTED]

(b) (4)

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

NDA 210828 for Gallium Ga 68 DOTA-TOC (Ga-68-DOTATOC) injection is a 505(b)(2) application with proposed indication for use with positron emission tomography (PET) for localization of somatostatin receptor (SSTR) positive neuroendocrine tumors (NETs). The clinical mass dose for ⁶⁸Ga-DOTATOC is not more than (b)(4) µg; therefore, this is a microdose application. The low mass dose precludes pharmacological activities. The nonclinical recommendations for such an application are limited based on the Guidance “Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations” (<https://www.fda.gov/media/107641/download>).

DOTATOC exhibited high affinity for somatostatin type 2 receptors based on in vitro binding assays using AR4-2j tumor membranes and with in vivo scanning of AR4-2J tumor bearing mice intravenously administered ⁹⁰Y-DOTATOC. Ga-68-DOTATOC binds to SSTRs, with highest affinity for subtype 2 receptors (SSTR2). It binds to cells that express SSTRs including certain malignant cells, which commonly overexpress SSTR2 receptors. Ga-68-DOTATOC distributes to all SSTR2-expressing organs such as normal pituitary, thyroid, spleen, adrenals, kidney, pancreas, prostate, liver, and salivary glands. There were no drug-related adverse effects observed in a 4-week rat intravenous toxicity study using once weekly doses of up to 250 µg/kg DOTATOC (~67-fold safety factor for the maximum clinical mass dose based on the human equivalent dose). No serious adverse reactions identified in three clinical studies and in a survey of the scientific literature

There were no nonclinical studies submitted to evaluate absorption, metabolism or excretion. Such studies are not typically required for microdose radiopharmaceutical agents. There were no nonclinical carcinogenicity data submitted such data is typically required only for drugs that are administered chronically). The Applicant requested a waiver for reproductive and developmental studies and this was granted.

The nonclinical review discipline recommends approval.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

The Applicant did not submit nonclinical pharmacology study reports. In the published literature submitted by the Applicant, unlabeled DOTATOC was shown to have high affinity ($IC_{50}=0.6nM$) to somatostatin receptors using AtT20 pituitary cell membranes in vitro (de Jong et al. 1998). Cold Y-DOTATOC was shown to have high affinity ($IC_{50}=2.4nM$) to somatostatin receptors (mostly SSTR2) using AR4-2J tumor membranes in vitro and ^{90}Y -DOTATOC showed favorable PET imaging characteristics in vivo when administered intravenously to AR4-2J tumor bearing mice (Froidevaux et al. 2000).

5.4. ADME/PK

Nonclinical pharmacokinetic (absorption, distribution, metabolism, excretion) study reports were not submitted.

5.5. Toxicology

5.5.1. General Toxicology

Subchronic Toxicity Study of Edotreotide by Intravenous Administration to CD® Rats/ Report # 31523

Key Study Findings

- Rats received weekly intravenous administration for 4 weeks of 0, 25, 75, or 250 $\mu g/kg$ DOTATOC. No drug-related adverse effects were observed in this study.

Conducting Laboratory and Location:

(b) (4)

GLP Compliance:

Yes

Table 5. Methods for Subchronic Toxicity Study in Rats

Methods	Details
Dose and frequency of dosing:	0 (vehicle) 25, 75, and 250 µg/kg administered as a single injection on days 1, 8, 15, and 22
Route of administration:	Intravenous
Formulation/Vehicle:	Solution/saline
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	10/sex/group
Age:	33 days males and 36 days females at initiation of dosing
Deviation from study protocol affecting interpretation of results:	No

Table 6. Observations and Results: Changes from Control in Subchronic Toxicity Study in Rats

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	No drug-related clinical signs noted.
Body weights	No drug-related effects on body weights.
Ophthalmoscopy	No drug-related ophthalmic findings.
ECG	N/A
Hematology	No toxicology significant drug-related effects
Clinical chemistry	No toxicology significant drug-related effects
Urinalysis	No toxicology significant drug-related effects
Gross pathology	Animals euthanized on day 23, no drug-related macroscopic findings.
Organ weights	No toxicology significant drug-related effects
Histopathology	No drug-related microscopic findings.
Adequate battery: Yes	
<i>Other evaluations</i>	No drug-related effects in a noise test (response to a sudden loud noise.

Abbreviation: ECG = electrocardiogram

General Toxicology; Additional Studies

The Applicant submitted an abstract of a single-dose toxicity rat intravenous study. There was insufficient information in the abstract to determine if the study was adequately designed (Venturella et al. 2015).

Nonclinical genetic toxicology and carcinogenicity data were not submitted.

5.5.2. Reproductive and Developmental Toxicology

The Applicant requested a waiver for reproductive and developmental toxicology studies. The waiver request is justified and should be granted.

6. Clinical Pharmacology

6.1. Executive Summary

At the Pre-NDA meeting held on October 3, 2017, it was agreed that this application would rely on the scientific literature to support the clinical pharmacology-related topics.

The recommended dose for adults is 4 mCi (148 MBq) with a range of 3 to 5 mCi (111 to 185 MBq) administered as an intravenous injection. In pediatric patients, the recommended dose is 0.043 mCi/kg of body weight (1.59 MBq/kg) with a minimum of 0.3 mCi (11.1 MBq) up to 3 mCi (111 MBq).

No formal dose finding studies for Ga-68-DOTATOC were conducted by the Applicant. However, the Applicant has listed 19 literature articles that have used Ga-68-DOTATOC with average doses ranging from 50 to 250 MBq. The adult dose for the three prospective studies was 4 mCi (148 MBq), with adjustments for the pediatric population (0.043 mCi/kg; minimum dose was 0.3 mCi and maximum dose was 3 mCi). At these dose levels the diagnostic performance of Ga-68-DOTATOC was acceptable. Therefore, the proposed dosing is acceptable for both adult and pediatric population.

Approximately 16% of the injected radioactivity was excreted in urine within 2 to 4 hours after injection. There is no information of Ga-68-DOTATOC distribution/pharmacokinetics (PK) in patients with hepatic or renal impairment in the submission.

The effective radiation dose resulting from the administration of 148 MBq (4 mCi of 68Ga-DOTATOC injection dose) to an adult weighing 75 kg, is about 3.11 mSv. For an administered activity of 148 MBq (4 mCi) the typical radiation doses to the critical organs, which are the urinary bladder wall, spleen, and kidneys/adrenals, are about 18, 16, and 12 mSv, respectively. Because the spleen has one of the highest physiological uptakes, higher uptake and radiation dose to other organs or pathologic tissues may occur in patients with splenectomy.

Non-radioactive somatostatin analogs competitively bind to somatostatin receptors and may affect Ga-68-DOTATOC imaging results. Short-acting somatostatin analogs must be discontinued 24 hours before imaging with Ga-68-DOTATOC and imaging should be performed just prior to dosing with long-acting somatostatin analogs.

Overall, based on the information submitted in this NDA, from the clinical pharmacology perspective, this NDA is approvable.

6.2. Summary of Clinical Pharmacology Assessment

No clinical pharmacology studies were conducted by the Applicant. However, the Applicant cited 24 literature references in support of the PK (mechanism of action, distribution, metabolism, excretion, and dosimetry) information. Thus, literature data support the clinical pharmacology content for this application and the package insert.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Ga-chelated DOTATOC exhibited essentially the same binding affinity ($2.5 \pm 0.5 \text{ nM}$) for human SSTR2 (somatostatin receptor subtype 2) as that of somatostatin ($2.7 \pm 0.3 \text{ nM}$) and octreotide ($2.0 \pm 0.7 \text{ nM}$). Ga-68-DOTATOC binds to cells that express somatostatin receptors including malignant cells, which overexpress SSTR2 receptors. Ga-68-DOTATOC distributes to all SSTR2-expressing organs such as pituitary, thyroid, spleen, adrenals, kidney, pancreas, prostate, liver, and salivary glands. Uptake in the lung and lymph nodes are lower as compared to SSTR2-expressing organs. SUV_{max} (standard uptake value maximum) values varied widely but had low variability within organ type. SUV_{max} values exclusively correlated with SSTR2 expression, whereas there was no correlation of SUV_{max} with the expression of the other four SSTR subtypes. One article reported significant correlation between increased Ga-68-DOTATOC uptake and increased IHC SSTR2 expression in biopsy tissue from NET patients but not SSTR3 or SSTR5.

No formal dose finding studies for Ga-68-DOTATOC were conducted by the Applicant. However, the Applicant has listed 19 literature articles that have used Ga-68-DOTATOC average doses ranging from about 50 to 250 MBq. The mean injected dose of Ga-68-DOTATOC across the studies was 121 MBq. The literature studies formed the basis of dose selection for three prospective studies conducted by the Applicant. The adult dose for all three prospective studies was about 4 mCi (148 MBq), with adjustments for the pediatric population (0.043 mCi/kg; minimum dose was 0.3 mCi and maximum dose was 3 mCi). Based upon the literature precedent and the Applicant's own studies with good sensitivity and specificity with 4 mCi dose, the proposed dose is acceptable. The effective radiation absorbed dose from 148 MBq (4 mCi) dose of Ga-68-DOTATOC is approximately 3.11 mSv (0.311 rem) in an adult.

For pediatric patients, a weight-based dose of: 1.591 MBq/kg (0.043 mCi/kg) with a minimum of 11.1 MBq (0.3 mCi) up to 111 MBq (3 mCi), as a bolus intravenous injection is acceptable.

According to the Applicant, the to-be-marketed formulation is identical to the formulation that was studied. Therefore, no biowaiver request is needed. One investigator reported the impact of unlabeled peptide mass upon quantitative binding of Ga-68-DOTATOC to somatostatin receptors. A total of six patients underwent three sequential PET/CT scans with intravenous injections of Ga-68-DOTATOC at 3-hour intervals preceded by 0, 50, and 250 or 500 μg of

unlabeled peptide (octreotide), administered 10 minutes before the tracer, Tracer uptake decreased at the higher peptide doses (250 and 500 μ g).

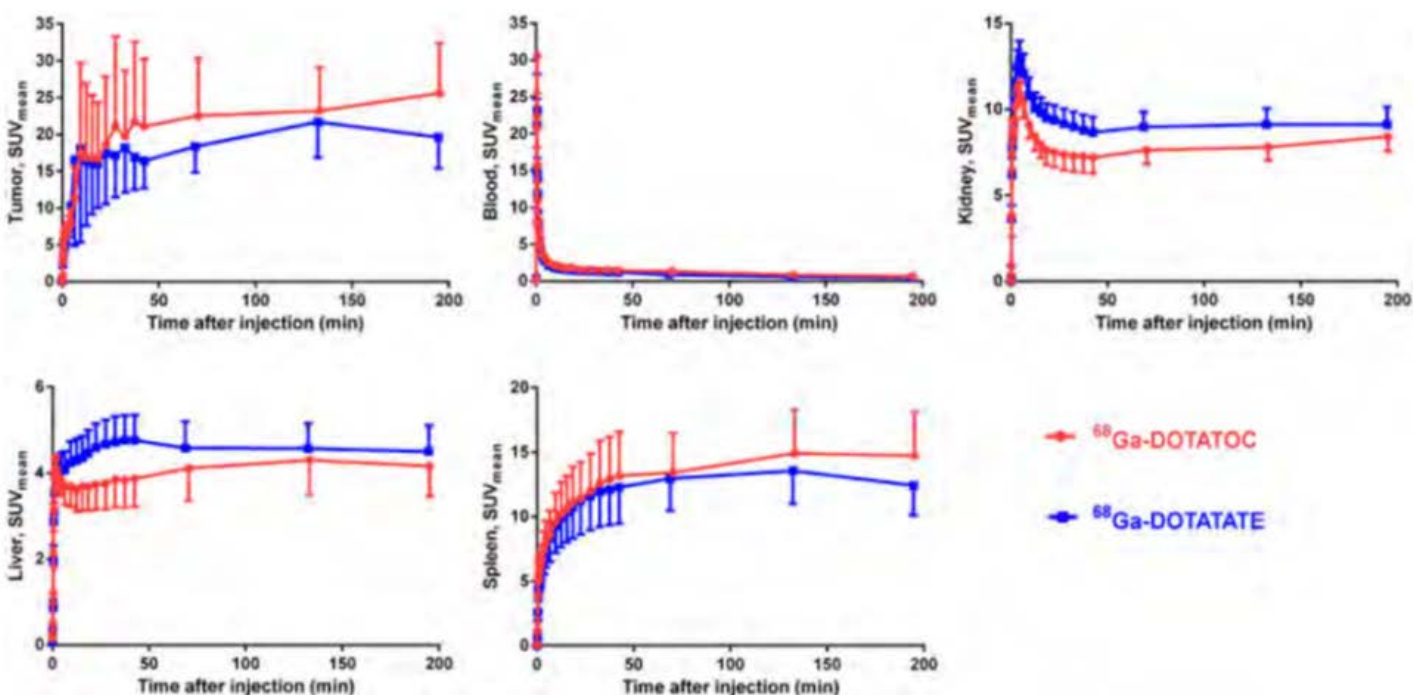
Ga-68-DOTATOC is cleared from the blood with bi-exponential decay and half-lives of 2 ± 0.3 and 48 ± 7 minutes. Within 4 hours, no radioactive parent or metabolites were detected in the serum. The highest uptake of Ga-68-DOTATOC was observed in spleen and kidney. Maximum uptake values (SUV_{max}) were higher in malignant compared to nonmalignant tissues. Accumulation in organs plateaued after 50 minutes. Kidney, liver, and lumbar spine all showed low retention by 38 minutes post-injection, whereas the tracer continued to accumulate in tumors with 95% of maximal activity occurring 50 to 90 minutes after injection, with a similar time course in the spleen. (b) (4)

Approximately 16% of the injected radioactivity was excreted in urine within 2 to 4 hours after injection. No metabolites were detected after 4 hours of administration. It should be noted that no studies were performed in patients with renal impairment or hepatic impairment.

Non-radioactive somatostatin analogs competitively bind to somatostatin receptors and may affect Ga-68-DOTATOC imaging results. Short-acting somatostatin analogs must be discontinued 24 hours before imaging with Ga-68-DOTATOC and image just prior to dosing with long-acting somatostatin analogs.

In one study, the PK of Ga-68-DOTATOC was compared to ^{68}Ga -DOTATATE in 100 tumors in 10 patients with metastatic NETs. Patients underwent one dynamic and three whole-body PET/CT scans at 1, 2, and 3 hours after injection with 87 ± 16 MBq Ga-68-DOTATOC or 92 ± 18 MBq ^{68}Ga -DOTATATE on two sequential days. PK blood samples were collected at 5, 20, 45, 60, 120, and 180 minutes after injection for measurement of whole-blood and plasma radioactivity concentrations. Urine was sampled as voided, and total volumes and radioactivity concentrations were measured. Blood Ga-68-DOTATOC radioactivity decreased to less than 4.7% of the peak level within 45 minutes of injection, and to 2.0% at 195 minutes post-injection (Figure 1). After 50 minutes, accumulation of Ga-68-DOTATOC in all organs reached a plateau. The tumor SUV_{max} and SUV_{mean} were higher at 2 hours than at 1 hour.

Figure 1. Time Activity Curves After Injection



Source: (Veliky et al. 2014)

Abbreviation: SUV = standardized uptake value

Dosimetry

The whole-body effective dose for administration of 100 to 112 MBq ^{68}Ga -DOTATOC was 0.021 to 0.023 mSv/MBq. The highest SUV at 60 to 180 minutes after injection was observed in the spleen, kidneys, liver, and bone marrow. Residence times (hours) for ^{68}Ga -DOTATOC were highest for liver (0.128 ± 0.041), kidney (0.048 ± 0.011), spleen (0.038 ± 0.023), and urinary bladder contents (0.086 ± 0.052). The highest absorbed doses were urinary bladder wall, spleen, kidney, adrenals, and liver as shown in Table 7.

Table 7. Estimated Radiation Absorbed Dose per Injection Activity in Selected Organs with Ga-68-DOTATOC

Site	Absorbed Dose (mGy/MBq)
Urinary bladder wall	0.119±0.058
Spleen	0.108±0.065
Kidney	0.082±0.020
Adrenal gland	0.077±0.028
Liver	0.041±0.014
Red marrow	0.016±0.003
Gallbladder wall	0.015±0.001
Total body	0.014±0.002
Lungs	0.007±0.001
Effective dose (mSv/MBq)	0.021±0.003

Abbreviations: MBq = megabecquerel, mGy = milligray, mSv = millisievert

The effective radiation dose resulting from the administration of 148 MBq (4 mCi of Ga-68-DOTATOC injection dose) to an adult weighing 75 kg, is about 3.11 mSv. For an administered activity of 148 MBq (4 mCi) the typical radiation dose to the critical organs, which are the urinary bladder wall, spleen, and kidneys/adrenals, are about 18, 16, and 12 mSv, respectively. Because the spleen has one of the highest physiological uptakes, higher uptake and radiation dose to other organs or pathologic tissues may occur in patients with splenectomy.

No radioactive metabolites were detected in serum within 4 hours after administration of Ga-68-DOTATOC. Radiotracer elimination is exclusively via urine. In the first 2 to 4 hours after injection, about 16% of Ga-68-DOTATOC activity was excreted in the urine.

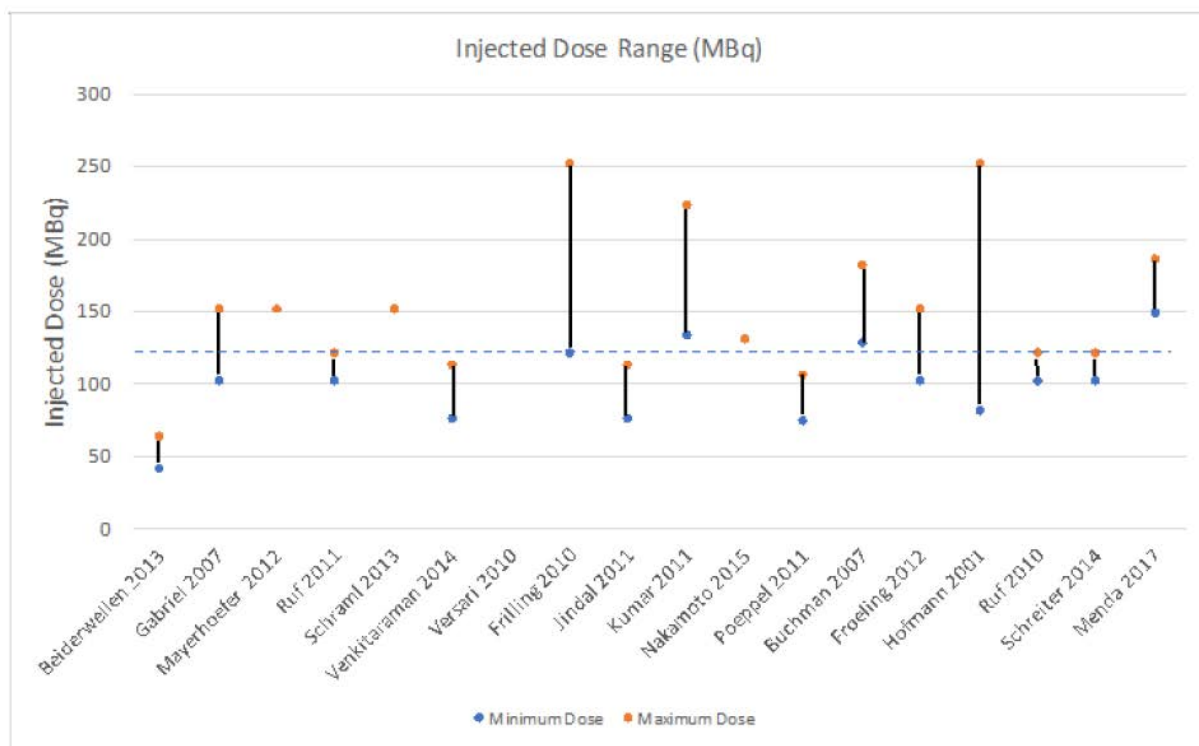
Overall, for this diagnostic agent, the exposures are acceptable and lower than for F-18-FDG, a commonly used diagnostic agent for PET imaging of patients with cancer.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant reported 19 articles from literature that had used various doses of Ga-68-DOTATOC. The range of doses (from about 50 to 250 MBq) for these literature articles is shown in Figure 2.

Figure 2. Ranges of Injected Dose of Ga-68-DOTATOC



Abbreviations: MBq = megabecquerel

The mean injected dose of Ga-68-DOTATOC across the studies was 121 MBq, slightly lower than the 148 MBq (4 mCi) dose used in RET-NET-01. The patient's size is the largest contributor to variability in scan quality. However, according to the Applicant, weight-based dosing only helps minimally.

For pediatric patients, the target dose was 0.043 mCi/kg (1.59 MBq/kg) with a range of 0.3 to 3 mCi (11.1 to 111 MBq) Ga-68-DOTATOC. RET-NET-01 included only 18 patients younger than 18 years. Dose by age in the study population is shown in Table 8; for pediatric patients, the dose per kg body weight is shown in Table 9.

Table 8. Dose Administered in RET-NET-01 By Age—Full Analysis Population

Variable	<2 years n=1	2 to <12 Years n=6	12 to <18 Years n=11	18 to <65 years n=256	≥65 years n=60
Dose (mCi)					
Mean ± SD	0.54	0.96±0.22	2.68±0.53	4.04±0.28	4.01±0.42
Median	0.54	0.93	2.84	4.00	4.01
Minimum	0.54	0.68	1.81	2.80	2.17
Maximum	0.54	1.21	3.58	4.86	4.74

Abbreviations: mCi = millicurie; n = number of patients in a specific group; SD = standard deviation

Table 9. Dose per Kilogram Administered by Age for Pediatric Patients—Full Analysis Population

Variable	<2 years n=1	2 to <12 Years n=6	12 to <18 Years n=11
Dose (mCi/kg)			
Mean ± SD	0.046	0.050±0.023	0.038±0.007
Median	0.046	0.042	0.040
Minimum	0.046	0.038	0.026
Maximum	0.046	0.097	0.045

Abbreviations: mCi = millicurie; n = number of patients in a specific group; SD = standard deviation

Overall, age had no impact on the clinical performance or safety of Ga-68-DOTATOC.

Therapeutic Individualization

There is no therapeutic individualization of dose for Ga-68-DOTATOC in adults. A flat dose of 4.0 mCi for adults is recommended for adults. This is acceptable, as it is consistent with the literature cited and the Applicant's data on imaging performance.

For pediatric patients, a weight-based dose is proposed: 1.591 MBq/kg (0.043 mCi/kg) with a minimum of 11.1 MBq (0.3 mCi) up to 111 MBq (3 mCi), as a bolus intravenous injection. This dose is acceptable based on the results of pediatric patients. The weight-based dosing allows minimum radiation exposure to the patient as compared to full adult dose.

Outstanding Issues

There are no outstanding issues from clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

See Sections 6.2.1. and 6.2.2.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Efficacy is not based directly on a biomarker or pharmacokinetics (exposure-response/imaging). However, Ga-68-DOTATOC uptake in tumors is due to binding to SSTR2 receptors expressed on NET. Clinical pharmacology information provides limited supportive evidence of effectiveness.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the general patient population for which the indication is being sought. See Section 6.2.2 above for details on dosing.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. No intrinsic factors were identified to affect the performance of the product. The safety and efficacy of Ga-68-DOTATOC has not been studied in patients with renal function impairment.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The product will be administered intravenously and, therefore, no effect of food is expected.

Glucocorticoids can down-regulate somatostatin receptor (SSTR) expression in human neuroendocrine tumors. In patients with ectopic Cushing's Syndrome (ECS, also known as hypercortisolism) SSTR expression may be downregulated, negatively influencing SSTR imaging. Thus, hypercortisolism normalization should be considered before performing 68Ga-DOTATOC PET.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant submitted two clinical datasets to support the safety and efficacy of Ga-68-DOTATOC:

1. RET-NET-01, a retrospective analysis of data from three prospectively conducted clinical studies and patient-level data:
 - Study 1: A Phase 1/2 study in 220 patients with known or suspected SSTR2 positive tumors.
 - Study 2: A Phase 2 study in approximately 62 patients with histologically proven NET or other SSTR2 positive tumors.
 - Study 3: A Phase 2 study in approximately 52 patients with SSTR2 positive tumors.
2. GRAHAM-2017, from 17 clinical publications on Ga-68-DOTATOC, selected by the Applicant and group-level data extracted from the publications (Graham et al. 2017).

Table 10. Clinical Trials Relevant to NDA

Trial Identity	NCT No	Trial Design	Regimen/route	Study Endpoints	Sample Size	Study Population	No of Centers & Countries
Prospective Studies to Support Efficacy and Safety							
Study 1	1619865	Open label, prospective, single center study of Ga68 Dotatoc in patients with known or suspected somatostatin positive tumors	3.96 ± 0.55 mCi, IV injection, mass dose < 50 microgram	1. Evaluate the efficacy for diagnosis, staging, and monitoring response to treatment 2. Determine if conventional imaging demonstrated equivocal evidence of tumor size and location in the same subjects. 3. Evaluate if the scan results had an effect on treatment decisions.	220	Known or suspected SSTR positive tumors	1 in USA
Study 2	1869725	Open label, prospective, single center study of Ga68 Dotatoc in patients with known somatostatin positive tumors	3.98 ± 0.68 mCi, IV injection, mass dose < 50 microgram	Comparison of the efficacy of Ga-68-DOTATOC PET/CT with Octreoscan plus high resolution contrast-enhanced CT and other conventional imaging for diagnosis and staging of NET and other SSTR positive tumors.	62	Histologically proven NETs or other SSTR positive tumors	1 in USA
Study 3	2441062	Open label, prospective, single center study of Ga-68 Dotatoc in patients with known or suspected somatostatin positive tumors	3.71 ± 0.66 mCi, IV injection, mass dose < 50 microgram	To assess the change in management of subjects based on findings of the scan.	52	SSTR positive tumors	1 in USA
RET-NET-01		Retrospective analysis of prospectively collected data in the Studies 1, 2 and 3.	3.92 ± 0.66 mCi, IV injection, mass dose < 50 microgram	Described as “sensitivity” and “specificity”	269 for efficacy, 334 for safety	Known or suspected somatostatin positive tumors	1 in USA
Other studies pertinent to the review of efficacy or safety							
17 papers review [3]		Ga-68 DOTATOC Imaging of Neuroendocrine Tumors: A Systematic Review and Meta-Analysis		Efficacy: sensitivity and specificity	300 for efficacy		Multiple

Source: Modified from tabular listing of all clinical studies and Prospective Studies Overall Study Design and Plan of Clinical Study Report: RET-NET-01

Abbreviations: CT = computed tomography, IV = intravenous, mCi = millicurie, NDA = new drug application; NET = neuroendocrine tumors, SSTR = somatostatin receptor

7.2. Review Strategy

The clinical and statistical review teams initially reviewed each individual study protocol of the three clinical investigations contributing data under the retrospective RET-NET-01 protocol.

The review team identified Studies 1 and 2 in the RET-NET-01 protocol as sufficiently reliable for inclusion in labeling to support efficacy. Both studies were prospectively designed for performance evaluation and featured reasonable alignment between planned and actual

enrollment at the time of analysis. In contrast, Study 3 was designed for evaluation of management decisions and enrollment was insufficiently complete (only 68 patients enrolled of 200 planned) to permit focus on management endpoints or reliance on this study for efficacy.

In addition, the publications identified in GRAHAM-2017 were not associated with new Applicant claims, prespecified protocols, or submission of patient-level data. Therefore, the review team did not rely on these publications for its findings. The Applicant's systematic review of the literature and meta-analysis, however, provides supportive evidence of the diagnostic performance of Ga-68-DOTATOC across multiple centers. Highlights of the meta-analysis are provided in section 8.1.4 of this review.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study RET-NET-01

Trial Design

Study RET-NET-01 was a prospectively-planned retrospective clinical study to evaluate the safety and efficacy of Ga-68-DOTATOC for use with positron emission tomography (PET)/computed tomography (CT) in patients with SSTR positive NETs. Study RET-NET-01 evaluated patients who participated in three ongoing prospective clinical studies at the University of Iowa Hospitals and Clinics, had information on their NET status available as defined in the RET-NET-01 protocol, and received Ga-68-DOTATOC injection. The most common site of pathology was small bowel and pancreas; 1 and 2 for NET grade.¹ Imaging dates were planned to range from February 2012 through September 14, 2016. A minimum of 200 patients were planned. The three clinical studies are also referred to as Study 1, Study 2, and Study 3 in this review. The ClinicalTrials.gov registry numbers of Study 1, Study 2, and Study 3 are NCT01619865, NCT01869725, and NCT02441062, respectively.

Table 11 summarizes the three prospective clinical studies. While the Applicant acknowledged that the three studies varied in overall design, the Applicant claimed in the protocol of Study RET-NET-01 that the patient populations are sufficiently consistent to allow for prospectively planned analysis. The Applicant did not clarify the rationale of combining Study 1, Study 2, and Study 3 instead of analyzing these studies separately.

¹ See Table 3.

Table 11. Summary of Three Prospective Clinical Studies

	Study 1	Study 2	Study 3
Study Design	Phase 1/2, SS, OL	Phase 2, SS, OL	Phase 2, SS, OL
Subject Scan Dates included in RET-NET-01	28 February 2012 through 17 September 2015	30 April 2013 through 06 October 2015	03 November 2015 through 13 September 2016
Study Goal	Demonstrate the safety and efficacy of Ga-68-DOTATOC as an accurate imaging technique for diagnosis, staging, and monitoring response to treatment in subjects with SSTR expressing tumors.	Compare sensitivity and specificity of Ga-68-DOTATOC PET/CT with Octreoscan plus high-resolution, contrast-enhanced CT for diagnosis and staging in neuroendocrine tumors and other SSTR positive tumors.	Evaluate the impact of Ga-68-DOTATOC PET-CT on management of subjects with SSTR positive tumors.
Enrollment¹	Planned: 112 ² Enrolled: 224 ³	Planned: 112 Enrolled: 68	Planned: 200 Enrolled: 68
Pre-specified Tumor Types Evaluated	SSTR positive tumors (known or suspected)	Known NET and other SSTR positive tumors	SSTR positive tumors
Comparator/ Standard of Truth	CT scans, MRI scans, [In-111]-Octreotide scans, ultrasounds, and x-ray plain film.	Composite gold-standard that includes conventional imaging modalities and clinical follow-up. ⁴	Pre-DOTATOC scan Clinical Management Plan
Study Endpoint(s)	1. Evaluate the efficacy of Ga-68-DOTATOC for diagnosis, staging, and monitoring response to treatment. 2. Determine if conventional imaging demonstrated equivocal evidence of tumor size and location in the same subjects. 3. Evaluate if the scan results had an effect on treatment decisions.	Comparison of the efficacy of Ga-68-DOTATOC PET/CT with Octreoscan plus high resolution contrast-enhanced CT and other conventional imaging for diagnosis and staging of NET and other SSTR positive tumors.	The primary end-point of the study is assessing the change in management of subjects based on findings of the Ga-68-DOTATOC PET/CT scan.

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging; NET = neuroendocrine tumor; PET = positron emission tomography; OL = open-label; SS = single site; SSTR = somatostatin receptor.

¹ Values provided for "Enrolled" are as of the data-collection date for this retrospective study.

² The protocol inaccurately reflects a planned enrollment of 112 subjects, as it was initially approved by the site IRB in 2012 to enroll up to 200 subjects. In 2015, the site IRB approved an increase in the number of subjects (n=227) to increase the number of pediatric subjects (10 planned) as well as to provide data needed for statistical considerations.

³ As of this report, no new subjects were being enrolled, however some subjects were still eligible for second scans.

⁴ The "gold-standard" comparison includes information, as available, from biopsy, baseline Octreoscan and diagnostic CT, Octreoscan visualization during study, positive bone lesion clearly visible on bone scan or MRI, or negative biomarkers.

Source: Table 1 in the clinical study report of Study RET-NET-01

Two nuclear medicine physicians (also referred to as readers) independently re-reviewed the Ga-68-DOTATOC PET/CT images for Study NET-RET-01. They were blinded to clinical data and other conventional clinical imaging. When the physicians did not reach agreement, they re-reviewed the images together to determine consensus in a blinded fashion. When they were unable to reach consensus, a third nuclear medicine physician read the images in a blinded fashion to determine the final consensus reading. When the third physician was not able to determine the final consensus reading, the reads were classified as indeterminate.

Comment: The protocol of Study RET-NET-01 had not been submitted to the Agency through pre-IND 125673 prior to its conduct; the Agency did not have the opportunity to discuss the study design and analysis with the Applicant. The Applicant did not submit data traceable to the pre-specified CRFs for individual Studies 1 to 3, so it cannot be verified whether all available or selective Ga-68-DOTATOC PET/CT images were re-reviewed for enrolled patients.

The performance data reviewed below and summarized in labeling reflect the pre-consensus PET interpretation of NET-RET-01 Reader 1 and Reader 2. These readers can be considered

blinded insofar as the NET-RET-01 protocol specified that determination of positive or negative PET status was to be made in the absence of the patient's clinical data, including other imaging. Protocol deficiencies relevant to the extent of reader blinding include lack of controls to promote independence between the identity of blinded and site readers and lack of controls to limit awareness of local Ga-68-DOTATOC referral patterns and associated NET prevalence estimates. The Applicant did not submit data obtained from site reads.

Study Endpoints

The protocol pre-specified co-primary sensitivity and specificity endpoints were not agreed upon by FDA and were based on consensus reads. Sensitivity was defined as the proportion of patients with positive NET disease who are identified as positive; specificity was defined as the proportion of patients without NET disease who are identified as negative.

The NET disease status determination was derived from a composite reference of pathology, Octreoscan or 68Ga-DOTATATE PET/CT imaging data, conventional imaging data, and chromogranin A and pancreastatin data. When there was not sufficient data in the study to establish a positive or negative NET disease status, the patient's NET disease status is considered indeterminate.

Comment: Using the Applicant's composite reference, some patients' disease statuses were identified as positive without pathology; therefore, to avoid misuse of terminology, the Applicant's so-defined "sensitivity" and "specificity" are referred to as the positive percent agreement and negative percent agreement, respectively, in Section 8.1.

Statistical Analysis Plan

The full analysis population was defined as all patients who participated in the three prospective studies at the University of Iowa and received a Ga-68-DOTATOC scan.

The efficacy analysis population was defined as all patients who participated in the three prospective studies at the University of Iowa, received a Ga-68-DOTATOC scan, and had sufficient study data to establish NET status. The efficacy analysis population is a subset of the full population that excludes patients without a positive or negative NET disease status determination based on the composite reference.

The one-sided exact binomial test was planned by the Applicant to test:

- H_0 : positive percent agreement based on consensus reads ≤ 0.80 versus
- H_1 : positive percent agreement based on consensus reads > 0.80

and

- H_0 : negative percent agreement based on consensus reads ≤ 0.70 versus
- H_1 : negative percent agreement based on consensus reads > 0.70

8.1.2. Study Results

Patient Disposition

Table 12 summarizes patient population sizes. A total of 259 patients were in the efficacy analysis population of Study RET-NET-01, the majority (68.3%) of which were from Study 1. Approximately 77.5% (259 out of 334), 80.5% (177 out of 220), 95.2% (59 out of 62), and 44.2% (23 out of 52) of the full populations were included in the efficacy populations for Study RET-NET-01, Study 1, Study 2, and Study 3, respectively.

The numbers of patients in the full populations (see Table 12) appeared much smaller, compared to the planned sample sizes (see Table 11), for Study 2 and Study 3. The efficacy dataset only includes information regarding patients' first exposures to DOTATOC.

Table 12. Summary of Population Sizes

	RET-NET-01 N (%)	Study 1 N (%)	Study 2 N (%)	Study 3 N (%)
Full population	334 (100)	220 (100)	62 (100)	52 (100)
Efficacy analysis population	259 (77.5)	177 (80.5)	59 (95.2)	23 (44.2)

Source: statistical reviewer's summary

Table of Demographic Characteristics

Table 13 summarizes patient demographics. There were more women than men in Study RET-NET-01, primarily from Study 1. The average age of the efficacy analysis population of Study RET-NET-01 was 54.4 years (standard deviation (SD) 14.6). The majority of the efficacy analysis population was white. Patients enrolled in Study 1, Study 2, and Study 3 appeared similar in age and race distributions.

Table 13. Demographic Characteristics, Efficacy Analysis Population

	RET-NET-01* N=259	Study 1* N=177	Study 2 N=59	Study 3 N=23
Sex, n (%)				
Female	142 (54.8)	103 (58.2)	30 (50.9)	9 (39.1)
Male	117 (45.2)	74 (41.8)	29 (49.1)	14 (60.9)

	RET-NET-01* N=259	Study 1* N=177	Study 2 N=59	Study 3 N=23
Age (years)				
Mean ± SD	54.4±14.6*	54.8±13.2*	55.3±16.0	48.7±19.7
Median	57.4	57.8	58.4	56.6
Min, Max	1.4, 81.8	3.9, 75.9	4.3, 81.8	1.4, 76.0
Age Group, n (%)				
<18 years	13 (5.0)	6 (3.4)	4 (6.8)	3 (13.0)
18 to <65 years	192 (74.1)	135 (76.3)	40 (67.8)	17 (73.9)
≥65 years	54 (20.9)	36 (20.3)	15 (25.4)	3 (13.0)
Race, n (%)				
Non-white	13 (5.0)	8 (4.5)	2 (3.4)	3 (13.0)
White	245 (94.6)	168 (94.9)	57 (96.6)	20 (87.0)
Missing	1 (0.4)	1 (0.6)	—	—

* In Study 1, the age of a patient aged 41 years was incorrectly input as 15 years in the original dataset. The error has been corrected by the statistical reviewer for the summary statistics in this table.

Source: Selected from Table 1 in the March 19, 2019 response to information request

Applicant's Efficacy Results

Table 14 presents the analysis results of Study RET-NET-01 provided by the Applicant. A total of four patients from Study 3 were classified as indeterminate for PET status, based on consensus read. These patients were not included in the efficacy analyses. For Study RET-NET-01, the positive percent agreement based on consensus reads was 92.1 (95% exact CI: 87.5%, 95.4%); the negative percent agreement based on consensus reads was 92.3 (95% exact CI: 81.5%, 97.9%). Among the 16 subjects that had positive NET disease status determinations, but negative consensus reads, 11, 2, and 3 subjects had NET disease status determined by histology, Octreoscan or 68Ga-DOTATATE PET/CT imaging data, and conventional imaging data, respectively.

Table 14. Study RET-NET-01 Efficacy Analysis Conducted by Applicant, Efficacy Analysis Population

	Condition Positive ^a	Condition Negative ^a
Test Outcome Positive, n	187	4
Test Outcome Negative, n	16	48
	Positive Percent Agreement = 92.12% (p<0.0001 ^b)	Negative Percent Agreement = 92.31% (p<0.0001 ^c)

Abbreviations: n = number of subjects in a specific group.

^a Indeterminate subjects were not included in the analysis.

^b p-value is calculated from the one-sided exact binomial test comparing H0 = 0.80 versus H1 >0.80.

^c p-value is calculated from the one-sided exact binomial test comparing H0 = 0.70 versus H1 >0.70.

Source: selected from Table 16 in the March 19, 2019 response to information request

Data Quality and Integrity

The electronic submissions of the study are located at:

- <\\cdsesub1\evsprod\NDA210828\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\management-of-neuroe\5352-stud-rep-uncontr\ret-net-01>
- <\\cdsesub1\evsprod\NDA210828\0000\m5\datasets\ret-net-01>
- <\\cdsesub1\evsprod\NDA210828\0011\m5\datasets\ret-net-01>

The data quality and analysis quality are adequate. The review team performed an independent review using the Applicant's submitted datasets and confirmed the Applicant's analysis results.

8.1.3. Assessment of Efficacy Across Trials

Primary Endpoints

Table 15 presents the efficacy analysis results by study and reader. The positive percent agreement and negative percent agreement appeared consistent across studies and readers.

Table 15. Efficacy Analysis by Study and Reader, Efficacy Analysis Population

Reader		Positive by Composite Reference [†]	Negative by Composite Reference [†]
Study 1, N=177			
Reader 1	Positive Identified by Reader	121	5
	Negative Identified by Reader	12	39
	Agreement (%) (95% CI*)	91.0 (84.8, 95.3)	88.6 (75.4, 96.2)
Reader 2	Positive Identified by Reader	120	6
	Negative Identified by Reader	13	38
	Agreement (%) (95% CI*)	90.2 (83.9, 94.7)	86.4 (72.7, 94.8)
Study 2, N=59			
Reader 1 ^a	Positive Identified by Reader	46	2
	Negative Identified by Reader	4	6
	Agreement (%) (95% CI*)	92.0 (80.8, 97.8)	75.0 (34.9, 96.8)
Reader 2	Positive Identified by Reader	46	2
	Negative Identified by Reader	5	6
	Agreement (%) (95% CI*)	90.2 (78.6, 96.7)	75.0 (34.9, 96.8)
Study 3, N=23			
Reader 1 ^c	Positive Identified by Reader	17	0
	Negative Identified by Reader	1	0
	Agreement (%) (95% CI*)	94.4 (72.7, 99.9)	NA
Reader 2 ^b	Positive Identified by Reader	18	0
	Negative Identified by Reader	1	0
	Agreement (%) (95% CI*)	94.7 (74.0 99.9)	NA
Study RET-NET-01, N=259			
Reader 1 ^d	Positive Identified by Reader	184	7
	Negative Identified by Reader	17	45
	Agreement (%) (95% CI*)	91.5 (86.8, 95.0)	86.5 (74.2, 94.4)

Reader		Positive by Composite Reference [†]	Negative by Composite Reference [†]
Reader 2 ^b	Positive Identified by Reader	184	8
	Negative Identified by Reader	19	44
	Agreement (%) (95% CI*)	90.6 (85.8, 94.3)	84.6 (71.9, 93.1)

^a One patient had a missing read (not included in the analysis).

^b Four patients had a missing read (not included in the analysis).

^c Five patients had a missing read (not included in the analysis).

^d Six patients had a missing read (not included in the analysis).

[†] The composite reference was based on pathology, Octreoscan or 68Ga-DOTATATE PET/CT imaging data, conventional imaging data, and chromogranin A and pancreastatin data.

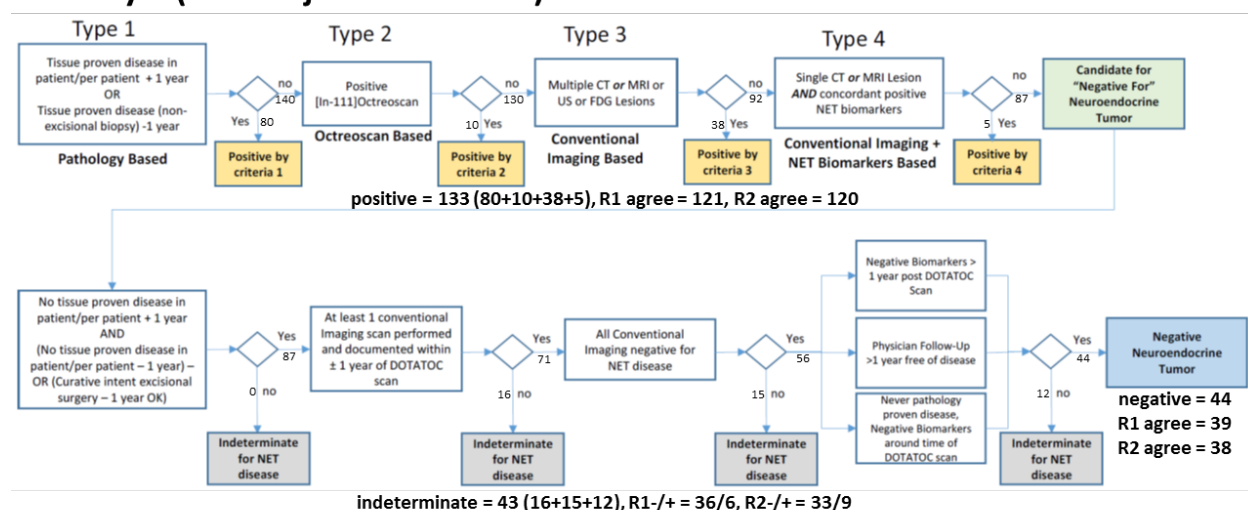
* Exact method

Source: Table 2 in the March 19, 2019 response to information request

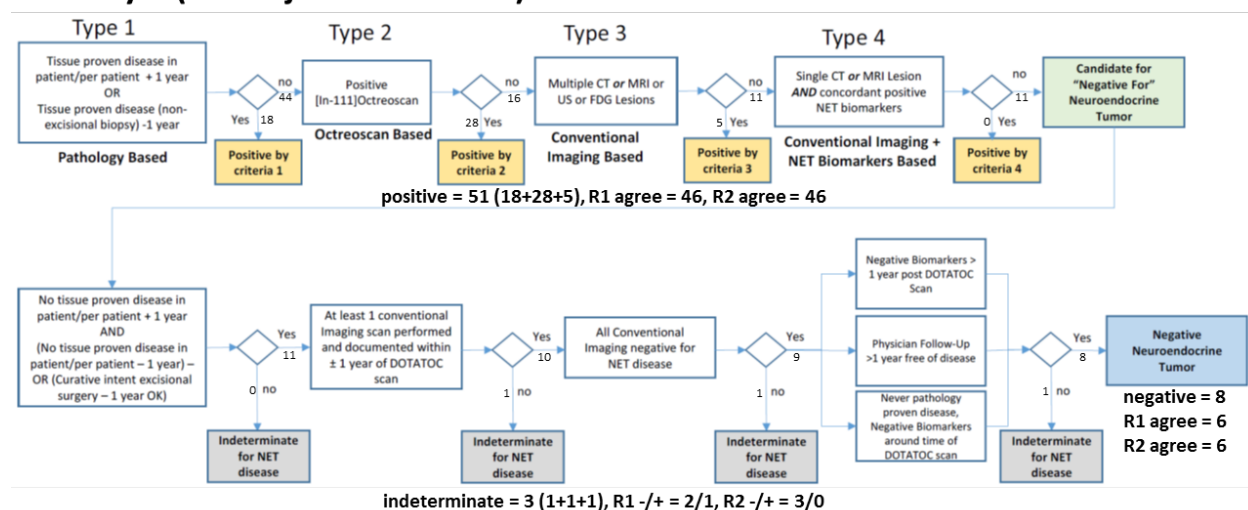
Figure 3 provides additional context for the above agreement estimates from Studies 1 and 2 (reflected in clinical labeling Section 14) according to the logic for positive vs. negative disease determination pre-specified in the RET-NET-01 protocol.

Figure 3. Efficacy Analysis by Logical Basis for Positive vs. Negative Disease Determination

Study 1 (220 subjects evaluated)



Study 2 (62 subjects evaluated)



Source: Review-team analysis of source data submitted under
 \\cdsesub1\evsprod\NDA210828\0009\m5\datasets\ret-net-01\analysis\legacy\datasets (see
 also “response-to-request-for-information” in Appendix).

Subpopulations

Table 16, Table 18, and Table 20 present the efficacy analysis results by age, sex, and race, respectively, based on reads by Reader 1. Table 17, Table 19, and Table 21 present the efficacy analysis results by age, sex, and race, respectively, based on reads by Reader 2. The pediatric sample size is too small to draw conclusions regarding this age group. Overall, the results are similar between readers. There is no compelling evidence from these subgroup analyses that

the adult or geriatric group benefits differently from Ga-68-DOTATOC. There is also no compelling evidence that a specific sex or race benefits differently from Ga-68-DOTATOC.

Table 16. Efficacy Analysis by Study and Age, Reader 1, Efficacy Analysis Population

Age Group	Reader 1	Positive by Composite Reference[†]	Negative by Composite Reference[†]
Study 1*, N=177			
Pediatric (<18 yr.) n=6	Positive Identified by Reader	2	0
	Negative Identified by Reader	1	3
	Agreement (%)	66.7	100.0
Adult (18 to <65 yr.) n=135	Positive Identified by Reader	89	4
	Negative Identified by Reader	10	32
	Agreement (%)	89.9	88.9
Geriatric (≥65 yr.) n=36	Positive Identified by Reader	30	1
	Negative Identified by Reader	1	4
	Agreement (%)	96.8	80.0
Study 2, N=59			
Pediatric (<18 yr.) n=4 ^a	Positive Identified by Reader	1	1
	Negative Identified by Reader	1	0
	Agreement (%)	50.0	0.0
Adult (18 to <65 yr.) n=40	Positive Identified by Reader	31	1
	Negative Identified by Reader	2	6
	Agreement (%)	93.9	85.7
Geriatric (≥65 yr.) n=15	Positive Identified by Reader	14	0
	Negative Identified by Reader	1	0
	Agreement (%)	93.3	NA
Study 3, N=23			
Pediatric (<18 yr.) n=3 ^a	Positive Identified by Reader	2	0
	Negative Identified by Reader	0	0

Age Group	Reader 1	Positive by Composite Reference [†]	Negative by Composite Reference [†]
Adult (18 to <65 yr.) n=17 ^c	Agreement (%)	100.0	NA
	Positive Identified by Reader	13	0
	Negative Identified by Reader	1	0
Geriatric (≥65 yr.) n=3 ^a	Agreement (%)	92.9	NA
	Positive Identified by Reader	2	0
	Negative Identified by Reader	0	0
	Agreement (%)	100.0	NA
Study RET-NET-01*, N=269			
Pediatric (<18 yr.) n=13 ^b	Positive Identified by Reader	5	1
	Negative Identified by Reader	2	3
	Agreement (%)	71.4	75.0
Adult (18 to <65 yr.) n=192 ^c	Positive Identified by Reader	133	5
	Negative Identified by Reader	13	38
	Agreement (%)	91.1	88.4
Geriatric (≥65 yr.) n=54 ^a	Positive Identified by Reader	46	1
	Negative Identified by Reader	2	4
	Agreement (%)	95.8	80.0

^a One patient had a missing read (not included in the analysis).

^b Two patients had a missing read (not included in the analysis).

^c Three patients had a missing read (not included in the analysis).

[†] The composite reference was based on pathology, Octreoscan or 68Ga-DOTATATE PET/CT imaging data, conventional imaging data, and chromogranin A and pancreastatin data.

* In Study 1, the age of a patient aged 41 years was incorrectly input as 15 years in the original dataset. The error has been corrected by the statistical reviewer for the summary statistics in this table.

Source: Table 3 in the March 19, 2019 response to information request, with errors corrected by the statistical reviewer

Table 17. Efficacy Analysis by Study and Age, Reader 2, Efficacy Analysis Population

Age Group	Reader 2	Positive by Composite Reference[†]	Negative by Composite Reference[†]
Study 1*, N=177			
Pediatric (<18 yr.) n=6	Positive Identified by Reader	2	0
	Negative Identified by Reader	1	3
	Agreement (%)	66.7	100.0
Adult (18 to <65 yr.) n=135	Positive Identified by Reader	88	6
	Negative Identified by Reader	11	30
	Agreement (%)	88.9	83.3
Geriatric (≥65 yr.) n=36	Positive Identified by Reader	30	0
	Negative Identified by Reader	1	5
	Agreement (%)	96.8	100.0
Study 2, N=59			
Pediatric (<18 yr.) n=4	Positive Identified by Reader	2	0
	Negative Identified by Reader	1	1
	Agreement (%)	66.7	100.0
Adult (18 to <65 yr.) n=40	Positive Identified by Reader	30	2
	Negative Identified by Reader	3	5
	Agreement (%)	90.9	71.4
Geriatric (≥65 yr.) n=15	Positive Identified by Reader	14	0
	Negative Identified by Reader	1	0
	Agreement (%)	93.3	NA
Study 3, N=23			
Pediatric (<18 yr.) n=3 ^a	Positive Identified by Reader	2	0
	Negative Identified by Reader	0	0
	Agreement (%)	100.0	NA

Age Group	Reader 2	Positive by Composite Reference [†]	Negative by Composite Reference [†]
Adult (18 to <65 yr.) n=17 ^b	Positive Identified by Reader	14	0
	Negative Identified by Reader	0	0
	Agreement (%)	100.0	NA
Geriatric (≥65 yr.) n=3	Positive Identified by Reader	2	0
	Negative Identified by Reader	1	0
	Agreement (%)	66.7	NA
Study RET-NET-01*, N=259			
Pediatric (<18 yr.) n=13 ^a	Positive Identified by Reader	6	0
	Negative Identified by Reader	2	4
	Agreement (%)	75.0	100.0
Adult (18 to <65 yr.) n=192 ^b	Positive Identified by Reader	132	8
	Negative Identified by Reader	14	35
	Agreement (%)	90.4	81.4
Geriatric (≥65 yr.) n=54	Positive Identified by Reader	46	0
	Negative Identified by Reader	3	5
	Agreement (%)	93.9	100.0

^a One patient had a missing read (not included in the analysis).

^b Three patients had a missing read (not included in the analysis).

[†] The composite reference was based on pathology, Octreoscan or 68Ga-DOTATATE PET/CT imaging data, conventional imaging data, and chromogranin A and pancreastatin data.

* In Study 1, the age of a patient aged 41 years was incorrectly input as 15 years in the original dataset. The error has been corrected by the statistical reviewer for the summary statistics in this table.

Source: Table 4 in the March 19, 2019 response to information request, with errors corrected by the statistical reviewer

Table 18. Efficacy Analysis by Study and Sex, Reader 1, Efficacy Analysis Population

Sex	Reader 1	Positive by Composite Reference[†]	Negative by Composite Reference[†]
Study 1, N=177			
Female n=103	Positive Identified by Reader	60	3
	Negative Identified by Reader	7	33
	Agreement (%)	89.6	91.7
Male n=74	Positive Identified by Reader	61	2
	Negative Identified by Reader	5	6
	Agreement (%)	92.4	75.0
Study 2, N=59			
Female n=30 ^a	Positive Identified by Reader	23	0
	Negative Identified by Reader	3	3
	Agreement (%)	88.5	100.0
Male n=29	Positive Identified by Reader	23	2
	Negative Identified by Reader	1	3
	Agreement (%)	95.8	60.0
Study 3, N=23			
Female n=9 ^a	Positive Identified by Reader	8	0
	Negative Identified by Reader	0	0
	Agreement (%)	100.0	NA
Male n=14 ^c	Positive Identified by Reader	9	0
	Negative Identified by Reader	1	0
	Agreement (%)	90.0	NA
Study RET-NET-01, N=259			
Female n=142 ^b	Positive Identified by Reader	91	3
	Negative Identified by Reader	10	36
	Agreement (%)	90.1	92.3
Male n=117 ^c	Positive Identified by Reader	93	4
	Negative Identified by Reader	7	9
	Agreement (%)	93.0	69.2

^a One patient had a missing read (not included in the analysis).

^b Two patients had a missing read (not included in the analysis).

^c Four patients had a missing read (not included in the analysis).

[†] The composite reference was based on pathology, Octreoscan or 68Ga-DOTATATE PET/CT imaging data, conventional imaging data, and chromogranin A and pancreastatin data.

Source: Table 5 in the March 19, 2019 response to information request

Table 19. Efficacy Analysis by Study and Sex, Reader 2, Efficacy Analysis Population

Sex	Reader 2	Positive by Composite Reference[†]	Negative by Composite Reference[†]
Study 1, N=177			
Female n=103	Positive Identified by Reader	62	4
	Negative Identified by Reader	5	32
	Agreement (%)	92.5	88.9
Male n=74	Positive Identified by Reader	58	2
	Negative Identified by Reader	8	6
	Agreement (%)	87.9	75.0
Study 2, N=59			
Female n=30	Positive Identified by Reader	23	0
	Negative Identified by Reader	4	3
	Agreement (%)	85.2	100.0
Male n=29	Positive Identified by Reader	23	2
	Negative Identified by Reader	1	3
	Agreement (%)	95.8	60.0
Study 3, N=23			
Female n=9 ^a	Positive Identified by Reader	7	0
	Negative Identified by Reader	1	0
	Agreement (%)	87.5	NA
Male n=14 ^b	Positive Identified by Reader	11	0
	Negative Identified by Reader	0	0
	Agreement (%)	100.0	NA
Study RET-NET-01, N=259			
Female n=142 ^a	Positive Identified by Reader	92	4
	Negative Identified by Reader	10	35
	Agreement (%)	90.2	89.7
Male n=117 ^b	Positive Identified by Reader	92	4
	Negative Identified by Reader	9	9
	Agreement (%)	91.1	69.2

^a One patient had a missing read (not included in the analysis).

^b Three patients had a missing read (not included in the analysis).

[†] The composite reference was based on pathology, Octreoscan or 68Ga-DOTATATE PET/CT imaging data, conventional imaging data, and chromogranin A and pancreastatin data.

Source: Table 6 in the March 19, 2019 response to information request

Table 20. Efficacy Analysis by Study and Race, Reader 1, Efficacy Analysis Population

Race	Reader 1	Positive by Composite Reference[†]	Negative by Composite Reference[†]
Study 1, N=177^a			
Non-white n=8	Positive Identified by Reader	4	0
	Negative Identified by Reader	1	3
	Agreement (%)	80.0	100.0
White n=168	Positive Identified by Reader	117	5
	Negative Identified by Reader	11	35
	Agreement (%)	91.4	87.5
Study 2, N=59			
Non-white n=2	Positive Identified by Reader	2	0
	Negative Identified by Reader	0	0
	Agreement (%)	100.0	NA
White n=57 ^b	Positive Identified by Reader	44	2
	Negative Identified by Reader	4	6
	Agreement (%)	91.7	75.0
Study 3, N=23			
Non-white n=3 ^b	Positive Identified by Reader	2	0
	Negative Identified by Reader	0	0
	Agreement (%)	100.0	NA
White n=20 ^c	Positive Identified by Reader	15	0
	Negative Identified by Reader	1	0
	Agreement (%)	93.8	NA
Study RET-NET-01, N=259^a			
Non-white n=13 ^b	Positive Identified by Reader	8	0
	Negative Identified by Reader	1	3
	Agreement (%)	88.9	100.0
White n=245 ^d	Positive Identified by Reader	176	7
	Negative Identified by Reader	16	41
	Agreement (%)	91.7	85.4

^a One patient has an unknown race and is not included in either analysis.

^b One patient had a missing read (not included in the analysis).

^c Four patients had a missing read (not included in the analysis).

^d Five patients had a missing read (not included in the analysis).

[†] The composite reference was based on pathology, Octreoscan or 68Ga-DOTATATE PET/CT imaging data, conventional imaging data, and chromogranin A and pancreastatin data.

Source: Table 7 in the March 19, 2019 response to information request, with errors corrected by the statistical reviewer

Table 21. Efficacy Analysis by Study and Race, Reader 2, Efficacy Analysis Population

Race	Reader 2	Positive by Composite Reference[†]	Negative by Composite Reference[†]
Study 1, N=177^a			
Non-white n=8	Positive Identified by Reader	4	0
	Negative Identified by Reader	1	3
	Agreement (%)	80.0	100.0
White n=168	Positive Identified by Reader	116	6
	Negative Identified by Reader	12	34
	Agreement (%)	90.6	85.0
Study 2, N=59			
Non-white n=2	Positive Identified by Reader	2	0
	Negative Identified by Reader	0	0
	Agreement (%)	100.0	NA
White n=57	Positive Identified by Reader	44	2
	Negative Identified by Reader	5	6
	Agreement (%)	89.8	75.0
Study 3, N=23			
Non-white n=3 ^b	Positive Identified by Reader	2	0
	Negative Identified by Reader	0	0
	Agreement (%)	100.0	NA
White n=20 ^c	Positive Identified by Reader	16	0
	Negative Identified by Reader	1	0
	Agreement (%)	94.1	NA
Study RET-NET-01, N=259^a			
Non-white n=13 ^b	Positive Identified by Reader	8	0
	Negative Identified by Reader	1	3
	Agreement (%)	88.9	100.0
White n=245 ^c	Positive Identified by Reader	176	8
	Negative Identified by Reader	18	40
	Agreement (%)	90.7	83.3

^a One patient has an unknown race and is not included in either analysis.

^b One patient had a missing read (not included in the analysis).

^c Three patients had a missing read (not included in the analysis).

[†] The composite reference was based on pathology, Octreoscan or 68Ga-DOTATATE PET/CT imaging data, conventional imaging data, and chromogranin A and pancreastatin data.

Source: Table 8 in the March 19, 2019 response to information request, with errors corrected by statistical reviewer

Table 22. NET Determination of Patients With or Without Known History of NET, Study 1

Study 1	Total N	NET Determination		
		Positive n	Negative n	Indeterminate n
Patients that had signs or symptoms but unknown history of NET	42	2	19	21
Patients with known history of NET	178	131	25	22

Abbreviation: NET = neuroendocrine tumor.

Source: statistical reviewer's summary

Comment: There was a clear difference in NET status for the subpopulation classified as having signs or symptoms but unknown history of NET (SNET, also referred to as “diagnostic indication” or “suspected NET,” compare positive to negative ratios across the two rows in Table 22, above). There was also a clear difference in PET status. Almost all SNET patients were found to be PET negative (in Study 1, for example, 38/41=93 and 36/41=88% for Readers 1 and Reader 2). In contrast, in patients with known history of NET, most were found to be PET positive (for example, in Study 1, 129/178=72% for Reader 1 and 130/178=73% for Reader 2). High rates of PET negativity in SNET patients have also been reported in the literature (Graham et al. 2017; Hope et al. 2018). In addition, the Applicant classified NET status as indeterminate in many SNET patients (21/42=50% in Study 1), excluding them from the efficacy population. The remaining SNET patients were classified as NET negative mostly because other imaging was identified within a year of Ga-68-DOTATOC PET and also classified as negative. Together, the available evidence on Ga-68-DOTATOC PET in the SNET subpopulation is sparse (with an inadequate number of NET positive cases, in particular), limited, and provides both low confidence in the performance and little clarity on the clinical meaningfulness of a negative PET scan, the likely result. This raises concerns about the need to conduct further testing in patients with a negative scan. For this purpose, a statement in the warnings section of the labeling will caution that negative scan after the administration of Ga 68 DOTATOC Injection in patients who do not have a history of NET disease might not rule out disease.

8.1.4. Literature Support

The Applicant conducted a meta-analysis of the literature from January 2000 to November 2015 (Graham et al. 2017). Seventeen publications relevant to clinical performance were selected for review. The papers were characterized based on type of data reported rather than population characteristics and fell into 5 groups:

- Sensitivity and specificity of Ga-68-DOTATOC (12 papers)

- Diagnosis of disease in patients with symptoms and biomarkers suggestive of NET but with negative conventional imaging (3 papers) Identification of unknown primary site in patients with metastatic NET (4 papers)
- Change in subsequent patient management (4 papers)
Comparison with Octreoscan (2 papers)

Several publications had information for more than one group, therefore, the total number of papers in the above groups are greater than the 17 publications selected for review by the Applicant.

Limitations of the literature and the meta-analysis include the following: most of the papers were retrospective; the majority of patients having biopsy-proven NET; trial design varied widely among the papers; and many papers had heterogeneous patient populations.

Nevertheless, the scientific literature provides ample supportive evidence of diagnostic performance across multiple centers. Overall, the literature review of the diagnostic performance of Ga-68-DOTATOC is considered supportive. Because of the limitations of the literature-, the review team did not verify nor rely on those results when determining the efficacy of Ga-68-DOTATOC. The review team identified Studies 1 and 2 in the RET-NET-01 protocol as sufficiently reliable for inclusion in labeling to support efficacy.

8.1.5. Integrated Assessment of Effectiveness

The findings from Studies 1 and 2 are consistent and support the efficacy of Ga-68-DOTATOC for localization of somatostatin receptor positive NETs in adult and pediatric patients.

8.2. Review of Safety

8.2.1. Safety Review Approach

Safety data were collected in all three prospective studies of RET-NET-01 and the AEs were integrated for the analysis of the drug safety. AEs were coded using standard Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 terminology (U.S. Department Of Health And Human Services 2010), and tabulated overall and by age, gender, race and tumor type (lesion sites). All safety evaluations (pre- and post-Ga-68-DOTATOC administration) were performed on the safety analysis set unless specified otherwise. For all safety assessments, baseline was defined as the last measure prior to the drug administration.

8.2.2. Review of the Safety Database

Overall Exposure

Clinical safety data from the RET-NET-01 study are from a total of 334 patients, of whom 18 were <18 years of age, 256 were between the ages of 18 and 65 years, and 60 were 65 years or older. The average age was 53.3 years (range: 1.4 to 81.8 years). Most patients (256) were within the 18 to <65 years of age group. There were slightly more women (190, 56.9%) than men (144, 43.1%). All but 17 (5.1%) patients were white (race for three patients was unknown). Neoplasms were located in various areas of the body. The safety database generally consisted of the spectrum of patients in the indicated population. See Table 23 below.

Table 23. Demographic Characteristics of Safety Analysis (N=334)

Demographic Parameters	n (%)
Gender	
Male	144 (43.1)
Female	190 (56.9)
Age	
Mean years (SD)	53.3±14.7
Median	57
Minimum	1.4
Maximum	81.8
Age group (year)	
<2	1 (0.3)
2 to <12	6 (1.8)
12 to <18	11 (3.3)
18 to <65	256 (76.7)
≥65	60 (18.0)
Race	
White	314 (94.0)
Non-white	17 (5.1)
Missing	3 (0.9)
Weight, kg	n=333
Mean years (SD)	88.8±23.0
Median	80.1
Minimum	11.7
Maximum	169.1

Demographic Parameters	n (%)
Tumor type, n (%)	
Carcinoid—origin unspecified	13 (3.9)
Lung	38 (11.4)
Metastasis	35 (10.5)
Pancreas	49 (14.7)
Small bowel	114 (34.1)
Other	40 (12.0)
None	43 (12.9)
Missing	2 (0.6)

Abbreviations: N = total number of patients; n = number of patients in a specific group;

SD = standard deviation

Source: Modified from RET-NET-01 Clinical Study Report, Table 7

The target dose for all three prospective studies was 4 mCi Ga-68-DOTATOC for adults and 0.043 mCi/kg for pediatrics. The study results are close to the study dose target, as shown in Table 24.

Table 24. Dose Overall and by Study—Full Analysis Population

Dose Variable (mCi)	RET-NET-01 N=334	Study 1 n=220	Study 2 n=62	Study 3 n=52
Mean ± SD	3.92±0.60	3.96±0.55	3.98±0.68	3.71±0.66
Median	3.98	4.02	4.06	3.89
Median	0.54	0.81	0.68	0.54
Maximum	4.86	4.06	4.84	3.99

Abbreviations: N = total number of patients; n = number of patients in a specific group;

SD = standard deviation

From: Clinical Study Report: RET-NET-01

Source: Listing 16.2.5.1

Adequacy of the Safety Database

The safety database submitted is adequate.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Based on the study protocols, safety data were collected and analyzed pre- and post-Ga-68-DOTATOC administration. See the patient safety monitoring procedure in Table 25 below.

Table 25. Procedures for Patient Safety Monitoring

	PET/CT Scan		Phone call Post 24 (18-36) hrs	Post 7 (7-28) days
	Predose	Postdose		
Medical History	X			
Concomitant Meds	X			
Physical Exam	X			X
Vital Signs* & Weight	X	X		X
Blood Tests**	X			X
Pregnancy Test	X			
Adverse Events	X	X	X	X

* Include blood pressure, heart rate, respiration rate and temperature

** Include complete blood count (CBC), differential, aspartate aminotransferase (AST), alanine transaminase (ALT), bilirubin, blood urea nitrogen (BUN), and creatinine

Source: Modified from Schedule of Study Events of the Study 1 of RET-NET-01

Abbreviations: CT = computed tomography, PET = positron emission tomography

Categorization of Adverse Events

The percentage of AEs was low and there was no individual AE reported in the RET-NET-01 study at a rate greater than or equal to 3% of the population studied. The most common AEs involved the gastrointestinal system.

Routine Clinical Tests

The Applicant reported that pre- and post-dose blood testing included complete blood count (CBC), differential, aspartate aminotransferase (AST), alanine transaminase (ALT), bilirubin, blood urea nitrogen (BUN), and creatinine, but no corresponding patient-level data were collected or submitted under the RET-NET-01 protocol.

8.2.4. Safety Results

The terms used to describe the degree of causality (attributability) between a medicinal product and adverse events include: certainly, probably, possibly, likely related, or not related. The terms probable, possible, unlikely and unrelated were used in the submission.

Of the 334 patients in the safety population, 50 (15%) reported 75 AEs. The majority (96%) of AEs were classified as Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 and were classified as unrelated (62.7%) to study drug. Most of the reported AEs were likely attributable to the patients' underlying disease. There were no individual AEs reported in the

RET-NET-01 study at a rate greater than or equal to 3%. The most frequently reported AEs include nausea (7), flushing (3), headache (3), pruritus (2), diarrhea (2) and abdominal pain (2) (see Table 26).

Table 26. Adverse Events with Probable and Possible Causality (N=334)

Subject ID	Study	AE and Timing	Causality		AE	%
			Probable	Possible		
(b) (6)	3	Nausea on D2		X	Nausea	2.1
	1	Nausea on D1		X		
	2	Nausea on D1		X		
	1	Nausea on D1		X		
	2	Nausea on D1		X		
	2	Nausea on D1		X		
	1	Nausea on D1		X		
	1	Flushing on D1	X		Flushing	0.9
	2	Flushing on D1		X		
	2	Flushing during injection on D1		X		
	1	Headache on D1		X	Headache	0.9
	1	Headache on D1		X		
	1	Headache on D1		X		
	1	Pruritus on D1		X	Pruritus	0.6
	1	Pruritus on D1		X		
	2	Diarrhea on D2		X	Diarrhea	0.6
	3	Diarrhea on D2		X		
	1	Abdominal pain on D1		X	Abdominal Pain	0.6
	2	Pain Dull burning sensation in head, throat, chest and abdomen. Resolved by end of PET scan on D1		X		
	3	Dizziness on D2		X	Dizziness	0.3
	3	Bloating on D2		X	Bloating	0.3
	1	Urticaria on forehead and chin during PET scan on D1		X	Urticaria	0.3

Source: Clinical team analysis from the NDA Database submitted; D1 and D2 refer to the same and next day, respectively, relative to Ga-68-DOTATOC administration

Deaths

The Applicant reported that no deaths or serious adverse events were documented in Studies 1 to 3 during the patient observation period.

Vital Signs

There were no abnormal vital signs indicative of a safety event. All parameters evaluated were within ranges expected for the patient population.

8.2.5. Analysis of Submission-Specific Safety Issues

Not applicable.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Analyses of adverse events by age (Table 27) and gender (Table 28) subgroups did not reveal any meaningful trends.

Table 27. Summary of Adverse Events by Age Group

			12 to <18	18 to <65	
	<2 Yrs	2 to <12 Yrs	Yrs	Yrs	≥65 Yrs
Adverse Events	n=1	n=6	n=11	n=256	n=60
Number of AEs	0	0	2	61	12
Patients with AEs, n (%)	0 (0)	0 (0)	2 (18.2)	41 (16)	7 (11.7)
AEs by CTCAE grade					
Grade 1	0 (0)	0 (0)	2 (100)	58 (95.1)	12 (100)
Grade 2	0 (0)	0 (0)	0 (0)	2 (3.3)	0 (0)
Grade 3	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)
AEs by relationship to study drug					
Probable	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)
Possible	0 (0)	0 (0)	0 (0)	18 (29.5)	4 (33.3)
Unlikely	0 (0)	0 (0)	0 (0)	3 (4.9)	2 (16.7)
Unrelated	0 (0)	0 (0)	2 (100)	39 (63.9)	5 (50)

Abbreviations: AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, N = number of patients, n = number of patients experiencing adverse events

Source: RET-NET-01 Clinical Study Report, Sections 14.2.2.3.1 and 14.2.2.3.2

There were too few patients in the two youngest age groups (<2 years and 2 to <12 years) for meaningful interpretation. There were two AEs reported by two patients 12 to <18 years. A total of 61 AEs was reported by 41 patients in the adult age group (18 to <65 years), and 12 AEs were reported by seven patients in the geriatric age group (≥65 years). In both age groups, nearly all AEs were designated as Grade 1 severity. Relationship of AEs to study drug was similar in both age groups with 29.5% of AEs in the adult age group and 33.3% of AEs in the geriatric group rated as possibly related to study drug. In the adult age group, one AE (flushing) was determined to be probably related to study drug. This was the only AE assessed as probably related across all age groups. The safety profile of Netspot (68Ga-DOTATATE) was also reported to be similar between adult and pediatric patients with SSTR positive tumors.

There was no meaningful difference in the proportion of male and female patients experiencing AEs (15.3% male, 15.8% female). Severity of AEs was similar for both genders with 100% of AEs reported by men and 93.2% of AEs reported by women classified as Grade 1. A small proportion of AEs reported by women were rated as Grade 2 (4.5%) and Grade 3 (2.3%) (see Table 28 below).

Table 28. Summary of Adverse Events by Gender

Adverse Events	Male n=144	Female n=190
Number of AEs	31	44
Patients with AEs, n (%)	22 (15.3)	30 (15.8)
AEs by CTCAE grade		
Grade 1	31 (100)	41 (93.2)
Grade 2	0 (0)	2 (4.5)
Grade 3	0 (0)	1 (2.3)
AEs by relationship to study drug		
Probable	0 (0)	1 (2.3)
Possible	5 (16.1)	17 (38.6)
Unlikely	3 (9.7)	2 (4.5)
Unrelated	23 (74.2)	24 (54.5)

Source: Summary of Adverse Events by Gender from Summary of Clinical Safety

Abbreviations: AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events

There were too few non-white patients for a meaningful subgroup analysis.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9. Additional Safety Explorations

Human Reproduction and Pregnancy

There are no studies with Ga-68-DOTATOC in pregnant women to inform any drug-associated risks; however, all radiopharmaceuticals, including Ga-68-DOTATOC, have the potential to cause fetal harm.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The review team did not identify any new or significant safety findings in the literature on Ga-68-DOTATOC, including the Applicant's published review (Graham et al. 2017).

The review team also investigated the postmarket experience for Netspot (68Ga-DOTATATE), approved on June 1, 2016. The Netspot applicant has submitted 10 Periodic Benefit-Risk Evaluation Reports (PBRER) and two annual reports to the FDA. According to the latest 10th PBRER submitted on December 10, 2018, up to (b) (4) patients may have been exposed in the postmarket setting. The following description has been added to the Postmarketing Experience section of the Netspot label (Food and Drug Administration 2018a):

- Gastrointestinal Disorders: Nausea and vomiting
- General Disorders and Administration Site Conditions: Injection site pain and burning sensation.

8.2.11. Integrated Assessment of Safety

The review team identified no major safety issue for Ga-68-DOTATOC based on integration across the Applicant's report under RET-NET-01 of safety data, published literature, and relevant postmarketing experience.

8.3. Statistical Issues

There were no apparent statistical issues in this application that affect the performance characteristics of Ga-68-DOTATOC for use with positron emission tomography for localization of somatostatin receptor positive NETs. Clinical context including the nature of patient population, the definition of standard of reference and its independence from Ga-68-DOTATOC PET imaging can affect statistical analyses for efficacy demonstration. The observed patient level positive and negative agreements demonstrated between NET status and Ga-68-DOTATOC PET imaging

appear to suggest Ga-68-DOTATOC efficacy when used as indicated for localizing SSR+ NETs in adult and pediatric patients.

8.4. Conclusions and Recommendations

The review team finds Ga-68-DOTATOC benefit-risk to be favorable and recommends approval for localization of somatostatin receptor positive NETs in adult and pediatric patients.

9. Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting and other external consultations for this NDA review.

10. Pediatrics

RET-NET-01 was a retrospective study that evaluated the data from 3 prospective studies conducted at the University of Iowa. All 3 studies included pediatric patients with total 18 pediatric subjects 1 - <18 years of age. There was no dose escalation study conducted and the pediatric dose is from adjustments of the adult dose. For pediatric subjects, the target dose was 0.043 mCi/kg (1.59 MBq/kg) with a range of 0.3-3 mCi (11.1-111 MBq) Ga-68-DOTATOC. At this dose, the diagnostic performance of the drug was acceptable. Therefore, the proposed pediatric dosage is acceptable. Full analysis of the dose per kg body weight of pediatric patient is shown Table 9.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The following represents a high-level summary of changes to the Applicant's proposed labeling.

Table 29. Prescribing Information Revisions

Applicant's Labeling	Agreed Labeling	Justification
Indications and Usage Ga-68 DOTATOC injection is indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) (b) (4) in adult and pediatric (b) (4) patients.	Ga-68 DOTATOC Injection is indicated for use with positron emission tomography (PET) for the localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients.	• (b) (4) •

Applicant's Labeling	Agreed Labeling	Justification
<u>Dosage and Administration</u> 2.2 Recommended Dosage and Administration Instructions <u>Recommended Dosage</u> In adults, the recommended amount of radioactivity to be administered for PET imaging is 4 mCi (148 MBq) with a range of 3 mCi to 5 mCi (111 MBq to 185 MBq) administered (b) (4).	2.2 Recommended Dosage and Administration Instructions <u>Recommended Dosage</u> In adults, the recommended amount of radioactivity to be administered for PET imaging is 4 mCi (148 MBq) with a range of 3 mCi to 5 mCi (111 MBq to 185 MBq) administered as an intravenous injection with an injection rate of approximately 10 seconds per mL. In pediatric patients, the recommended amount of radioactivity to be administered for PET imaging is 0.043 mCi/kg of body weight (1.59 MBq/kg) with a range of 0.3 mCi (11.1 MBq) to 3 mCi (111 MBq) as an intravenous injection with an injection rate of approximately 10 seconds per mL.	• (b) (4) provide the amount, rate, or size of the observation/effect. The Applicant provided a rate of 1 mL per 10 seconds. This could not be verified by Clinical Pharmacology in the clinical trials, however, from a clinical perspective this seems reasonable. • With a concentration of 0.5 mCi/mL to 4 mCi/mL, the infusion might go over 10 seconds to 80 seconds depending on the specific activity. Either way, image acquisition occurs at 60 minutes post injection and the rate should not affect efficacy.
New Section Added	2.3 Use with Somatostatin Analogs and Patient Hydration <u>Somatostatin Analogs</u> Somatostatin analogs bind to the same somatostatin receptors as Ga-68 DOTATOC Injection • Discontinue short-acting somatostatin analogs 24 hours before imaging with Ga-68 DOTATOC Injection. • Image patients with Ga-68 DOTATOC Injection just prior to dosing with long-acting analogs of somatostatin [see Drug Interactions (7.1)]	• Repetitive information was deleted throughout. • Section 2.3 was revised to add information regarding somatostatin analogue use / instructions for patients before administration, in alignment with information already contained in Section 7.1 Drug Interactions.

Applicant's Labeling	Agreed Labeling	Justification
Warnings and Precautions 5.2 Risk for Misinterpretation The uptake of Ga-68-DOTATOC reflects the level of somatostatin receptor density in NETs. However, uptake can also be seen in a variety of other tumor (b) (4) Increased uptake might also be seen in other pathologic conditions (b) (4) or might occur as a normal physiologic variant (e.g. uncinata process of the pancreas). (b) (4)	Warnings and Precautions 5.2 Risk for Image Misinterpretation The uptake of Ga 68 DOTATOC Injection reflects the level of somatostatin receptor density in NETs; however, uptake can also be seen in a variety of other tumors that also express somatostatin receptors. Increased uptake might also be seen in other non-cancerous pathologic conditions that express somatostatin receptors including thyroid disease or in subacute inflammation, or might occur as a normal physiologic variant (e.g. uncinata process of the pancreas) [see <i>Dosage and Administration</i> (2.5)] A negative scan after the administration of Ga 68 DOTATOC Injection in patients who do not have a history of NET disease does not rule out disease [see <i>Clinical Studies</i> (14)]	• The section, including the title, was updated for accuracy, clarifying that there may be uptake in other tumors that express SSTR and physiologic conditions. • (b) (4) • "A negative scan after the administration of Ga 68 DOTATOC Injection in patients who do not have a history of NET disease does not rule out disease" <u>was added</u> to reflect our concern about the performance of the drug in patients with suspected NET (see 8.1.3 Assessment of Efficacy Across Trials, Subpopulations). Subpopulations). Because of the small study size and the small subpopulation of patients with suspected NET, it was difficult to characterize the performance in these patients.

Applicant's Labeling	Agreed Labeling	Justification
Warnings and Precautions 	Warning deleted	Deleted theoretical warning. 21 CFR 201.57 (c)(6) – this section should contain warnings about true adverse reactions not theoretical adverse reactions.
6 Adverse Reactions 	Clinical Trial Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Ga-68 DOTATOC injection was evaluated in 334 patients in clinical trials of patients receiving a single dose of Ga-68 DOTATOC injection for imaging known or suspected NET. The following adverse reactions occurred at a rate of <2%: <i>Gastrointestinal Disorders</i>: nausea The following adverse reactions occurred at a rate of a <1% <i>Skin and Subcutaneous Tissue Disorders</i>: pruritus <i>Vascular Disorders</i>: flushing	- The statement, is promotional. Only adverse reactions (AR) as defined in 21 CFR 201.57(c)(7) should be included. - Statement on the Significance of Adverse Reaction Data Obtained from Clinical Trials (from the Adverse Reactions Section of Labeling Guidance for Industry). - Adapted Adverse Reaction frequency and type from the ret-net-01 report, Table 44.

Applicant's Labeling	Agreed Labeling	Justification
Section 14 is not able to be presented in total. High-level changes are captured.		
14 Clinical Studies (b) (4)	• The safety and efficacy of Ga-68 DOTATOC Injection were established in two single-center, open-label studies (Study A and Study B) in which 282 patients with known or suspected SSTR-positive NETs received a single dose of Ga-68 DOTATOC. • Study A (study 1 in RET-NET-01) was presented by reader performance compared to composite reference (b) (4). The performance was described in absolute numbers and “percent agreement” (with composite reference). Presentation of • Study B (study 2 in RET-NET-01) was presented as descriptive.	• Study 1 and Study 2 from RET-NET-01 protocol are included in labeling. We reviewed the totality of the evidence presented and, based on the strength of the data, presented only these studies in the prescribing information. These are labeled “Study A” and “Study B.” Study 3 from RET-NET-01 is not included. • (b) (4) • (b) (4) • We do not agree to including information on (b) (4)

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Applicant's Labeling	Agreed Labeling	Justification

(b) (4)

12. Risk Evaluation and Mitigation Strategies

There is substantial safety information concerning this product. A risk evaluation and mitigation strategy are not needed.

13. Postmarketing Requirements and Commitment

There are no post-marketing requirements or commitments for this application.

14. Office Director (or Designated Signatory Authority) Comments

Introduction

Some NETs up-regulate somatostatin type 2 receptors (SSTR2)² which can be identified and located with imaging tests using peptides that preferentially bind to these receptors. 68Ga-DOTATOC consists of the radionuclide Ga-68 chelated to dodecanetetraacetic acid (DOTA) which is conjugated to octreotide (tyrosine substituted for phenylalanine at the 3 position of octreotide: Tyr3-octreotide or TOC). Ga-68-DOTATOC PET binds to SSTR2 and reports from the medical literature suggest that it is an effective test to locate NETs in the body. The ability to detect a NETs with Ga-68-DOTATOC will depend on up regulation of SSTR2, the density of the SSTR2 on the tumor cell and the size of the individual tumors given the limits of detection with PET imaging. Tumors without SSTR2 upregulation or smaller than the detection limits may not be detected by this test. The Applicant notes that “ (b) (4)

”³.

Benefit Risk Assessment

The Applicant has provided sufficient information to support the ability of Ga-68-DOTATOC PET to detect NETs in patients. There are no significant safety signals.

Efficacy and Safety Information

The Applicant submitted two types of information in support of the efficacy and safety of 68Ga-DOTATOC: 1) a retrospective analysis (Study RET-NET-01) of the 3 prospective studies conducted at a single center, the University of Iowa University Hospitals and Clinics (UIHC); and 2) a meta-analysis summarizing clinical trials from the literature but without any individual data provided. The UIHC study report did not provide lesion level data for each individual patient but instead focused on identifying whether the test could correctly identify the disease status of patients who had already been diagnosed with or without NETs. Typically, lesion level data would be evaluated in assessing the performance characteristics of the test. The Applicant has approached this differently in its presentation of the data. The Applicant does not provide information to quantify the amount of disease for each patient. Because of this, we are unable to comment on the limits of detection for individual lesions – which becomes important in

² Poorly differentiated NETS are less likely to have up regulation of SSTR2

³ Page 11 of 108 in RET-NET-01 report body document

assessing progression or regression of disease. This data is likely available but has not been provided and is not part of this application.

UIHC Study (Study RET-NET-01)

The Applicant conducted 3 studies at the UIHC and combined those studies together for a retrospective assessment of the data using 2 readers (board certified nuclear medicine physicians) to assess whether the test was positive or negative for diagnosing patients whose NETs status was known using a diagnostic algorithm (discussed later). The readers were blinded to both clinical data and other conventional clinical imaging for Ga-68-DOTATOC imaging interpretation. Only when there was not concurrence of the interpretation of the 2 readers, a third reader would be employed to make an assessment. For patients where a consensus was not reached by the readers, their scans were deemed indeterminate. The three prospective studies included in this retrospective assessment were:

1. Study 1: Safety and efficacy of Ga-68-DOTATOC positron emission tomography (PET) for diagnosis, staging, and measurement of response to treatment with somatostatin receptor positive tumors. (NCT:01619865; IND 114,398 serial #0000; IRB approval (b) (4))
2. Study 2: Comparator study of Ga-68-DOTATOC PET/CT with Octreoscan + high-resolution, contrast-enhanced CT for diagnosis and staging in neuroendocrine tumors and other somatostatin receptor positive tumors.⁴ (NCT:01869725; IND 114,398 serial #0001; IRB approval (b) (4))
3. Study 3: Impact of Ga-68 DOTATOC PET/CT on management of somatostatin receptor positive tumors. (NCT:02441062 IND; 114,398 serial #0003; IRB approval (b) (4))

Although it seems that these studies are disparate in their purpose, they did allow for the determination of disease using the truth standard identified by the Applicant.

The following table lists the different populations identified in the study. Although 334 patients were enrolled in this study and provided safety data, the efficacy analysis will focus on the “efficacy” population of 269 patients.

⁴ Nonendocrine tumors that express high levels of somatostatin receptors include breast and ovarian cancers, osteosarcomas, glioblastoma multiforme, meningiomas, gastric and hepatocellular carcinomas, and colorectal malignancies [from Module 2 Common Technical Document 2.5. Clinical Overview]

Table 6 Number of Subjects in Each Analysis Population Overall and by Study

Analysis Set	RET-NET-01 N	Study 1 n (%)	Study 2 n (%)	Study 3 n (%)
Full	334	220 (65.87)	62 (18.56)	52 (15.57)
Safety	334	220 (65.87)	62 (18.56)	52 (15.57)
Efficacy	269	184 (68.40)	59 (21.93)	26 (9.67)
Change in Management	52	0 (0.0)	0 (0.0)	52 (100.0)
Physician Reader	304	220 (72.37)	62 (20.39)	22 (7.24)
Tissue Pathology	145	96 (66.21)	22 (15.17)	27 (18.62)
OctreoScan	85	25 (31.65)	54 (68.35)	0 (0.0)

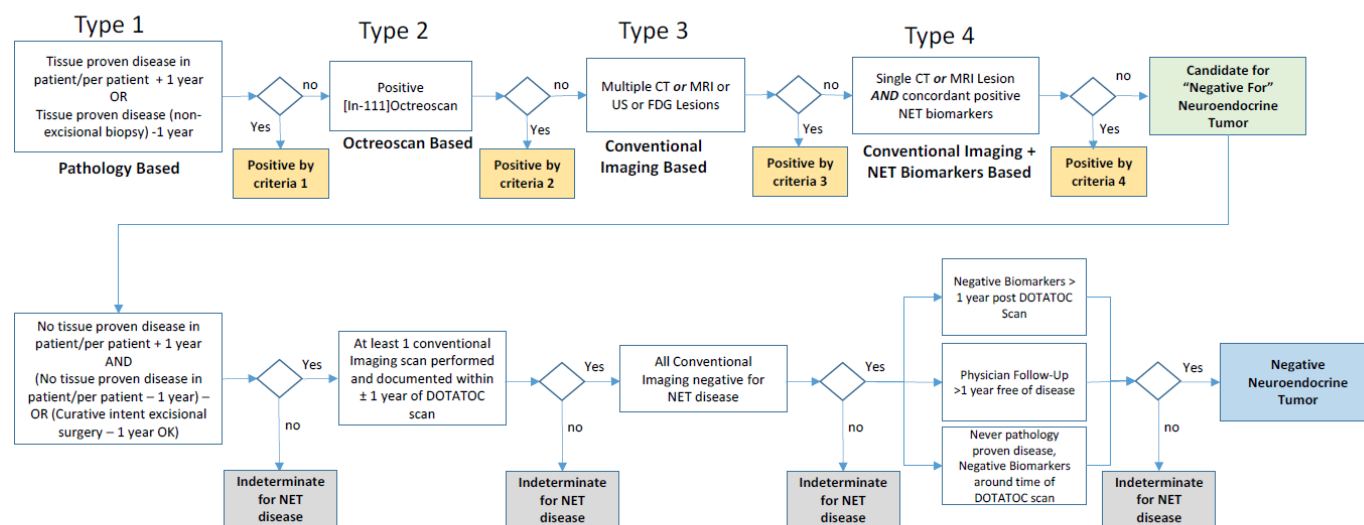
Abbreviations: N = total number of subjects; n = number of subjects in a specific group.

Source: Listing 16.2.3.

Standard of Truth (Study RET-NET-01)

The standard of truth was a 4-fold assessment of NET positivity or negativity. This assessment included evaluation of results from pathology, [In-111] Octreoscan imaging, conventional imaging (CT, magnetic resonance imaging, or fluorodeoxyglucose PET/CT), and blood biomarkers (chromogranin A and pancreastatin). There was a hierarchical sequence for deciding whether a patient had disease. The data in the application provided for each patient included the readers interpretation of the Ga-68-DOTATOC PET results as positive or negative for disease. The following figure illustrates the algorithm used to define the truth standard criteria for positive or negative disease designation.

Figure 2 Flowchart for the Determination of Type 1, Type 2, Type 3, and Type 4 Positive or Negative for NET Disease



Abbreviations: CT = computed tomography; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; NET = neuroendocrine tumor; US = ultrasonography.

Two-hundred and sixty-nine patients had a truth standard for NET disease and were included in the efficacy analysis population. The following table shows the number of patients who were characterized as positive based on the criteria (types) as defined above in the flowchart.

Table 14 Final Positive for NET Disease Determinations by Type for the Efficacy Analysis Population

Type (Classification Criteria)	Positive
Total, n (%)	214 (79.55)
Type 1 (Pathology), n (%)	125 (58.41)
Type 2 (OctreoScan), n (%)	36 (16.82)
Type 3 (Conventional Imaging), n (%)	52 (24.3)
Type 4 (Conventional Imaging plus Biomarkers), n (%)	1 (0.47)

Abbreviations: n = number of subjects in a specific group.

Patients who were designated as negative for NET disease for the truth standard were done so based on the following categories. The majority were given that designation based only on conventional imaging alone.

Table 15 Final Negative for NET Disease Determinations for the Efficacy Analysis Population

Type (Classification Criteria)	Negative
Total, n (%)	55 (20.45)
Excisional Biopsy, OctreoScan, and Conventional Imaging, n (%)	2 (3.64)
Excisional Biopsy and OctreoScan, n (%)	3 (5.45)
Excisional Biopsy and Conventional Imaging, n (%)	8 (14.55)
OctreoScan and Conventional Imaging, n (%)	6 (10.91)
Excisional Biopsy Alone, n (%)	0 (0)
OctreoScan Alone, n (%)	2 (3.64)
Conventional Imaging Alone, n (%)	34 (61.82)

Abbreviations: n = number of subjects in a specific group.

The primary efficacy analysis only included patients where a definitive diagnosis of disease status was made. Sensitivity and specificity were the primary efficacy endpoints for the retrospective study but are not defined as we typically expect it to be for the evaluation of performance characterization. Sensitivity was defined as the proportion of subjects with positive NET disease who were identified as positive by the Ga-68-DOTATOC scan as determined by a consensus read of the readers. Specificity was defined as the proportion of subjects without NET disease who were identified as negative by the Ga-68-DOTATOC scan as determined by the consensus read of the readers. The FDA reviewers have changed the description of this from sensitivity and specificity to positive percent agreement and negative percent agreement. The point estimates (expressed in percentages) and the 2-sided 95% exact CI were calculated. Indeterminate subjects were not included in the primary efficacy analysis. The positive percent agreement was 91% (p<0.0001, 95% CI: 87%, 95%). The negative percent agreement was 92% (p<0.0001, 95% CI: 82%, 98%).

Safety (Study RET-NET-01)

There were no significant safety events identified in the study.

Change in Management (Study RET-NET-01)

Change in clinical management was evaluated prospectively for the population in Study 3, which was designed to evaluate the comparison of a proposed clinical management plan with the clinical management plan determined after Ga-68-DOTATOC PET/CT results were revealed. Fifty-two patients were included in this study population. The Applicant reported that 31 of 52 had a major change in clinical management as illustrated in the following table⁵.

Table 17 Change in Clinical Management – Change in Management Population

Population	Total	Major Change	Estimate	95% CI	p-value*
Overall	52	31	59.62%	(45.10%, 72.99%)	<0.0001
Adult	48	28	58.33%	(43.21%, 72.39%)	<0.0001
Pediatric	4	3	75.00%	(19.41%, 99.37%)	0.0508

Abbreviations: CI = confidence interval.

* p-value is calculated from the one-sided exact binomial test comparing H0: CoM = 0.25 versus H1: CoM >0.25.

Further information was provided on the extent of disease detected by the Ga-68-DOTATOC relative to the extent of disease from the baseline data to support the original management plan. As the following table⁶ shows, 27 patients had either more extensive (N = 22) or less extensive (N = 5) disease. This number is less than the number of patients who reportedly had a major change in management based on the data in table 17 above.

Table 18 Extent of Disease Based on Ga-68-DOTATOC Image Evaluation – Change in Management Population

Extent of Disease	
Total, N	52
Less Extensive, n (%)	5 (9.62)
More Extensive, n (%)	22 (42.31)
No Change, n (%)	25 (48.08)

Abbreviations: N = total number of subjects; n = number of subjects in a specific group.

⁵ Table 17 from page 50 of RET-NET-01 Report Body

⁶ Table 18 from page 51 of RET-NET-01 Report Body

The change in management data is problematic for several reasons. First, just about any change in management was deemed to be a major change⁷. Second, specific data on what was observed in the Ga-68-DOTATOC scan and how that differed from previous baseline scans, conventional imaging or SPECT, that served as the basis for the original treatment plan, were not provided in the application. Third, it is not clear what baseline testing was done for each patient to support the initial management plan. (b) (4)

Pediatric Patients (Study RET-NET-01)

Seventeen⁸ pediatric patients were included in the retrospective full study population but only 14 were included in the efficacy population. Pediatric patients, unlike adult patients were dosed based on weight. The following table lists the mean dose and range of doses administered to pediatric and adult patients.

Table 38 Dose Administered by Age – Full Analysis Population

Variable	<2 years n = 1	2 - <12 years n = 6	12 - <18 years n = 11	18 - <65 years n = 256	≥65 years n = 60
Dose (mCi)					
Mean ± SD	0.54	0.96 ± 0.22	2.68 ± 0.53	4.04 ± 0.28	4.01 ± 0.42
Median	0.54	0.93	2.84	4.00	4.01
Minimum	0.54	0.68	1.81	2.80	2.17
Maximum	0.54	1.21	3.58	4.86	4.74

Abbreviations: n = number of subjects in a specific group; SD = standard deviation.

The following table lists the dose per kg of body weight administered to pediatric patients.

Table 39 Dose per Kilogram Administered by Age for Pediatric Subjects – Full Analysis Population

Variable	<2 years n = 1	2-<12 years n = 6	12-<18 years n = 11
Dose (mCi/kg)			
Mean ± SD	0.046	0.050 ± 0.023	0.038 ± 0.007
Median	0.046	0.042	0.040
Minimum	0.046	0.038	0.026
Maximum	0.046	0.097	0.045

Abbreviations: n = number of subjects in a specific group; SD = standard deviation.

⁷ Table 4 on page 27 of the RET-NET-01 Study report shows 10 possible management plans in a 10 x 10 table. 85% of the possible changes were considered major and 6% were considered minor.

⁸ Note: one patient was incorrectly listed as a 15-year-old patient and was in fact 41 years of age. Some tables may reflect 18 pediatric patients but in fact there were only 17.

The following table shows the efficacy for pediatric patients. The pediatric scan read results are similar to those obtained in adult patients.

Scan Results for Pediatric Patients in the Efficacy Population

Ga-68-DOTATOC	Truth Standard	
	Disease Positive	Disease Negative
Scan Positive	6	0
Scan Negative	2	5
	Positive percent agreement 75.00% (34.91%, 96.81%)	Negative percent agreement 100% (47.82%, 100%)

Note: one patient had an indeterminant read and is not included.

The Applicant has proposed a dose of 0.043 mCi/kg for pediatric patients.

Patients in Efficacy Population with Octreoscan and Ga-68-DOTATOC Scans Performed (Study RET-NET-01)

The Applicant provided an analysis of 34 patients who had NET disease status determined by pathology and an Octreoscan performed within 1 year of the Ga-68-DOTATOC scan. The sensitivity and specificity of both the Octreoscan and Ga-68-DOTATOC test were calculated⁹. The point estimate for the sensitivity was 96.6% for Ga-68-DOTATOC and 79.3% for Octreoscan but the 95% confidence intervals overlap.

There is a problem with this analysis because it excludes 45 patients from the efficacy population who also had an Octreoscan performed but had their disease status determined by criteria other than pathology. They were not included in the Applicant's analysis. Seventy-nine patients in the efficacy population with their disease status determined by the algorithm had both an Octreoscan¹⁰ and Ga-68-DOTATOC scan performed. The following tables provides the results for the sensitivity and specificity for Octreoscan and the positive and negative percent agreement for the Ga-68-DOTATOC scan. Another deficiency is that the timing of the scans could have been as great as one year apart.

⁹ from page 54 of RET-NET-01 Report Body

¹⁰ acquired within 1 year of the Ga-68-DOTATOC PET/CT scan (page 21 of 108 in RET-NET-01 report body document)

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(Ga-68-DOTATOC)

Octreoscan	Truth Standard	
	Disease Positive	Disease Negative
Scan Positive	59	0
Scan Negative	7	13
	Sensitivity* 59/66 = 89.3%	Specificity* 13/13 = 100%
*Sensitivity and specificity are used because the Octreoscan results were based on the review of the medical records and did not undergo a retrospective read with 2 readers.		

Ga-68-DOTATOC	Truth Standard	
	Disease Positive	Disease Negative
Scan Positive	63	1
Scan Negative	3	12
	Positive percent agreement 63/66 = 95.4%	Negative percent agreement 12/13 = 92.3%

It is important to note that this data is based on a per patient analysis. There is some suggestion in the literature that Ga-68-DOTATOC may be more sensitive in identifying lesions than Octreoscan. The data provided in the submission did not attempt to evaluate individual lesion counts per patient and as such we are not able to evaluate this.

Medical Literature (Meta-Analysis Provided by the Applicant)

The information supporting the non-clinical and clinical pharmacology of this application was based on data from the medical literature as discussed in those sections of this memo. In addition to their retrospective clinical study (Study RET-NET-01), the Applicant also submitted supporting data that included their published systemic review (Graham 2017)¹¹ of clinical trial studies with information relevant to sensitivity and specificity, studies comparing the lesion detection rates of Ga-68-DOTATOC and 111In Octreotide and change in management studies. The authors acknowledged that these studies involved the clinical management of NETs

¹¹ J Nucl Med 2017; 58:1452–1458

patients and “in most of the papers the reference standard is suboptimal, or biased and no rigorous safety studies have been done”. They note that the results are consistent in the studies and that safety issues were not an issue with the use of the drug.

In the systemic review, seven studies were identified where sensitivity and specificity were calculated for the detection of NETs disease. They ranged in size from 8 to 84 patients. The truth standard varied between studies but included a combination of histopathology and a variety of combinations of imaging tests such as CT scan, MRI, esophageal ultrasound. The sensitivity ranged from 80.0 % to 97.6% and specificity ranged from 66.7% to 100.0%. Five other studies were identified, enrolling 13 – 52 patients, where all patients had NETs diagnosis. Ga-68-DOTATOC detected lesions in all of these patients. Overall, the results from published literature are consistent with the observation from the Applicant’s retrospective clinical study conducted at UIHC.

Two studies compared the detection rate for Ga-68-DOTATOC compared to In-111-Pentetreotide. The time separating the conduct of the tests was 2 – 4 weeks in one study and $\leq$ 60 days in the other. In both studies, more lesions were detected with 68Ga DOTATOC. The Applicant did not submit individual lesion data for their Study RET-NET-01 (b) (4)

15. Appendices

15.1. References

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15.2. Financial Disclosure

According to the submission, the RET-NET-01 and the meta-analysis studies were conducted at a single study center, UIHC-PET Imaging Center. There were three investigators who led as principal investigator (PI) and participated in the studies of Ga-68-DOTATOC.

Investigators

Investigator Name	Company	Participating Study
(b) (6)	UIHC-PET Imaging Center	(b) (6) RET-NET-01
	UIHC-PET Imaging Center	(b) (6) the meta-analysis of 17 publications on Ga-68 DOTATOC
	UIHC-PET Imaging Center	(b) (6) Study 1 Study 2 Study 3

Source: Selected from submission Form FDA 3454; Certification: Financial interests and arrangements of clinical investigators

All three investigators had financial disclosures documents in the submission. The Applicant has not entered into any financial arrangement with the three investigators whereby the value of compensation to the investigators could be affected by the outcome of the studies. No listed investigators were the recipient of significant payments of other sorts.

15.3. Nonclinical Pharmacology/Toxicology

15.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.5. Additional Clinical Outcome Assessment Analyses

None.

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/s/

DIANE C HANNER
08/20/2019 12:06:11 PM

RONALD HONCHEL
08/20/2019 12:10:21 PM

ADEBAYO A LANIYONU
08/20/2019 12:11:41 PM

SAM HABET
08/20/2019 01:12:07 PM

CHRISTY S JOHN
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SUE JANE WANG
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ALEXANDER GOROVETS
08/20/2019 02:27:50 PM
For Dr. Louis Marzella

ALEXANDER GOROVETS
08/20/2019 02:27:50 PM
For Dr. Louis Marzella

CHARLES J GANLEY
08/21/2019 07:24:35 AM