CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208547Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences

Secondary Statistical Review and Comments

Clinical Studies

NDA Number:	208547
Supplement Number:	00
Drug Name:	^{68}Ga-DODATATE
Applicant:	Advanced Accelerator Applications
Submitted date:	01 July 2015
Review Due Date:	11 December 2015
Review Priority:	Priority (Orphan Drug Designated Product)
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Keywords:	Sensitivity, Specificity, Diagnostic, Meta-analysis

Reference ID: 3860537

1 Executive Summary

1.1 The Submission and Findings

This review is intended to supplement the information provided by the primary statistical reviewer.

The sponsor provided published literature, a meta-analysis of the literature findings and the results of one prospective clinical study to support the following indication: "^{68}Ga-DODATATE is a radioactive diagnostic agent indicated for (b) (4)

After reviewing the literature and the clinical study reports and protocol, the following findings are noted:

- The meta-analysis provided by the sponsor should not be considered in regulatory decision making.
- Two of the studies cited in the literature provide useful information with respect to estimating the diagnostic performance of ^{68}Ga-DODATATE . See performance estimates below.
- The prospective clinical study data are difficult to interpret due to study design issues.

1.2 Conclusion

The literature provided support the use of the product as and aid to determining the presence of NET in patients suspected of having NET, as described in Haug 2012 and as an aid in determining recurrence of NET, as described in Haug 2014. The data and analyses provided in Srirajaskanthan 2010 support using ^{68}Ga-DODATATE as an adjunct in diagnosing NET.

Whether the evaluable studies are adequate to support the indication is a clinical determination.

2 VUMC 2015

This study is described by the sponsor as a prospective, phase I/II single center, open label study to assess the safety and efficacy of ^{68}Ga-DODATATE . Patients were selected from those who were being seen at one center for the treatment of NET. Of note is one inclusion criterion listed in the protocol:

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Known diagnosis of classical neuroendocrine tumor, such as medullary thyroid
cancers, typical or atypical (bronchial, thymic or gastrointestinal) carcinoid tumors,
pancreatic neuroendocrine tumors, patients with neuroendocrine metastases from
an unknown primary tumor, or patients with clinical ‘‘carcinoid syndrome’’ and
elevated blood markers (e.g. chromogranin A, plasma serotonin levels, etc.)
characteristic of neuroendocrine tumors with no known primary tumor.
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Also of note is the exclusion from analyses of 19 enrolled patients not having previously undergone pentetreotied scans. Study participants underwent ^{68}Ga-DODATATE imaging after

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screening and baseline assessments. Reading of ^{68}Ga-DODATATE images was done using consensus reading and in some cases third reader adjudication. Readers then reviewed all other available imaging to evaluate possible treatment implications that might be associated with addition of ^{68}Ga-DODATATE scanning.

Ninety-seven patients were enrolled and 78 were included in the full analysis set, 19 being excluded for lack of viable pentetreotide scans.

The sponsor reported estimates of sensitivity and specificity for ^{68}Ga-DODATATE are: Se=96.0%, 95%CI (86.3%, 99.5%) and Sp=92.9%, 95%CI (76.5%, 99.1%).

The sponsor reported estimates of sensitivity and specificity for ^{111}In-pentetriotide are: Se=72.0%, 95%CI (57.5%, 83.8%) and Sp=89.3%, 95%CI (71.8%, 97.7%).

The estimates of sensitivity and specificity were reported to have been determined with respect to a reference standard consisting of disease state (cancer or benign). The reference standard is not well defined in the submission because of the inclusion criterion described above which requires a patient to be known to have NET to enter the study making the existence of true negatives within the study difficult to interpret.

3 Literature Support

3.1 Meta-Analysis

The meta-analysis provided by the sponsor should not be considered in the evaluation of ^{68}Ga-DODATATE for regulatory purposes because the component studies are inadequate for the purpose.

Out of the eight studies chosen for the meta-analysis, four (Haug, 2009; Alonso, 2014; Kayani, 2008; Wild, 2013) included no "true negative" patients. Although the sponsor interprets the study by Srirajaskanthan 2010 in a way that provided specificity estimates, the estimates do not include a comparison to the patients' true medical condition [NET/no NET] and therefore are not valid for the purpose of estimating specificity. A study of diagnostic performance should include both truly positive and truly negative patients in order to provide performance estimates that can be evaluated in context. It is generally advisable to evaluate a test through both sensitivity and specificity because adjusting the cut point of the test can result in very high values of one and very low values of the other. Consider the trivial example in which a reader calls all images positive. Such a reader will have 100% sensitivity and 0% specificity. If there are no true negative patients in the sample being studied, the only estimate available is that of [100%] sensitivity. Study reports with no specificity estimates to contrast against the sensitivity estimates, or vice-versa are questionable. In addition to this problem, readers have been shown to change their "cut-points" as the prevalence of positive images in the study sample changes. considering the lack of specificity estimates, the meta-analysis depending on these studies should not be considered reliable.

The study by Hoffman 2012 should not be considered for regulatory purposes for the reasons stated below. The exclusion of these literature sources leaves only the two selected papers by Haug and the VAMC study. Pooling of the Haug data is not advised as they result

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from studying different populations (suspected NET vs recurrent NET). These papers are considered separately below.

3.2 Haug 2012

This study is a retrospective study of 104 consecutive patients who at the time of imaging were suspected of having NET or showed some biomarker based suspicion of NET. Of the 104 patients, 36 were histologically diagnosed with NET, the remaining 68 were considered non-NET patients.

The estimates of sensitivity and specificity for ^{68}Ga-DODATATE were calculated from this data and reported by the sponsor to be: Se=81%, 95%CI (64%, 92%) and Sp=90%, 95%CI (80%, 96%).

The limitations of this study include the use of consensus reading for ^{68}Ga-DODATATE which may not correspond to clinical practice and the possibility that there is selection bias present in choosing the 104 consecutive patients in the study.

It is a clinical judgment as to whether or not the diagnostic performance of the product in this setting is adequate.

3.3 Haug 2014

The purpose of this retrospective study was to evaluate the diagnostic performance of ^{68}Ga-DODATATE in detection of recurrent NETs. The study is a retrospective study of 63 consecutive patients who had a history of resection of the primary NET without suspicion of residual disease, and also had no proved evidence of NET recurrence. The presence or absence of recurrent NET was determined through histopathology (25/63) or follow-up (38/63). Twenty-nine of the 63 patients were determined to have recurrent NET.

The estimates of sensitivity and specificity for ^{68}Ga-DODATATE in detecting recurrent NET were calculated and reported by the sponsor to be: Se=90% [26/29] and Sp=82% [28/34]. Note that no confidence intervals were found for these estimates in the body of the sponsor's submission and the performance estimates provided for this study accompanying the meta-analysis in a later section were in error. Therefore, FDA calculated the following estimates with score confidence intervals: Se=89.7%, 95%CI (73.6%, 96.4%) and Sp=82.4%, 95%CI (66.5%, 91.7%).

In the discussion section of the paper, the authors note that estimated sensitivity and PPV markedly decreased when the reader were unaware of patient clinical information. Other limitations of the study include use of consensus reading for ^{68}Ga-DODATATE which may not correspond to clinical practice and the possibility that there is selection bias present in choosing the 63 consecutive patients in the study.

It is a clinical judgment as to whether or not the diagnostic performance of the product in this setting is adequate.

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3.4 Srirajaskanthan 2010

Fifty-one patients of 312 being followed for NET treatment at one site were selected to be in this study. The 51 were chosen based on [^{111}In-DTPA-octreotide] scintigraphy results that were negative or showed only low uptake of tracer. All 51 had a histologically confirmed diagnosis of NET. These 51 patients were referred to have ^{68}Ga-DODATATE PET scans.

The study authors compared consensus reading by two readers using ^{68}Ga-DODATATE to cross-sectional imaging and the ^{111}In-DTPA-octreotide imaging and reported that 87.2% [41/47] of the ^{68}Ga-DODATATE images agreed with positive findings on cross-sectional imaging and no false positive findings. It appears that the sponsor used these findings as sensitivity and specificity in the meta-analysis. These findings are not reliable estimators of sensitivity and specificity because the study selected only NET positive patients by histology [no histologically negative patients]. Since the study included no negative patients specificity cannot be estimated. A more reasonable point estimate of sensitivity from this study would be 41/51 [80%].

The study authors conclude that ^{68}Ga-DODATATE detected 74% of lesions in a selected group of patients with negative or faint uptake of ^{111}In-DTPA-octreotide . This finding supports the claim that the method has adjunctive value.

3.5 Hoffman 2012

This retrospective study included review of 59 out of 76 consecutive patients having ^{68}Ga-DODATATE scans at on site. Forty-one patients were shown to have NET through biopsy, 11 patients were suspected of having NET and seven were determined to be non-NET patients. The lack of final patient status with respect to NET for the 11 patients listed as suspected of having NET makes estimating diagnostic performance metrics difficult and unreliable. Therefore this study should not be considered in evaluation the diagnostic performance of ^{68}Ga-DODATATE for regulatory purposes.

4 References

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6. Kayani I, Bomanji JB, Groves A, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and 18F-FDG. Cancer 2008;112(11):2447-55

7. Srirajaskanthan R, Kayani I, Quigley AM, et al. The role of 68Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on 111In-DTPA-Octreotide scintigraphy. J Nucl Med 2010;51:875-82.

8. Wild D, Bomanji JB, Benkert P, et al. Comparison of 68Ga-DOTANOC and 68Ga-DOTATATE PET/CT within patients with gastroenteropancreatic neuroendocrine tumors. J Nucl Med 2013;54:364-72.

Reference ID: 3860537

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/s/

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12/15/2015

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12/16/2015

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation
Clinical Studies

NDA/BLA	NDA 208-547
Drug Name:	[redacted] (b) (4) (Kit for the Preparation of ^{68}Ga-DOTATATE for Injection)
Proposed Indication(s):	Diagnostic for [redacted] (b) (4) neuroendocrine tumors [redacted] (b) (4) NETs)
Applicant:	Advanced Accelerator Applications (AAA)
Date(s):	NDA Submission: July 1, 2015 PDUFA Date: March 1, 2016
Review Priority:	Priority (Orphan Drug Designated Product)
Biometrics Division:	
Statistical Reviewer:	Satish C. Misra, Ph. D.
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Keywords: Sensitivity, Specificity, Efficacy, Safety, Confidence Interval, Meta-Analysis, Random Effect Model

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1. EXECUTIVE SUMMARY

The application contains a prospective comparative study (VUMC) that shows that the sensitivity of ^{68}Ga-DOTATATE (96% [95% CI: 86, 100] was significantly superior to the sensitivity of comparator product ^{111}In-pentetreotide [72% CI: 58, 84]. The specificity of two product was similar 93% [95% CI 77, 99] for ^{68}Ga-DOTATATE vs. 89% [95% CI 72, 98] for ^{111}In-pentetreotide. %). A systematic review of literature and meta-analysis showed that the pooled sensitivity based on meta-analysis for ^{68}GaDOTATE was 90% with 95% CI (86 – 100%) and the pooled specificity was 90% with 95% CI (84% - 95%). These results show support for approval of the product for an indication for imaging in the detection of somatostatin receptor bearing GEP-NETS.

This was a 505(b)(2) NDA submission based on a survey of abstracts of recent scientific and medical literature conducted to identify areas of current interest in ^{68}Ga-DOTATATE from a clinical perspective. The sponsor is seeking an indication for (b) (4) The data submitted was a literature review. A systematic review was conducted on PubMed, a service of the US National Library of Medicine. This included the Medline and Toxline core databases. This resulted in 13 studies that met all the inclusion criteria and were used for the final analysis.

The primary analysis planned per meta-analysis protocol was a direct comparison of ^{68}Ga-DOTATATE and Octreoscan based on testing for non-inferiority of the two summary receiver operator characteristic (SROC) areas by a one sided chi-square test. However, the number of publications fulfilling the inclusion/exclusion criteria of the literature review was limited. Due to the lack of adequate published data, a direct comparison of ^{68}Ga- DOTATATE and ^{111}In-pentetreotide (primary analysis) planned in the meta-analysis protocol and Statistical Analysis Plan (SAP)) was not possible. Therefore, sponsor stated that the selection of a non-inferiority margin was not necessary. (Note: this was not communicated to the agency any time prior to information request by the Agency). The sponsor submitted SAP, Agency reviewed it but before the Agency could send the comments to the sponsor, the NDA was submitted.

Therefore, the sponsor focused on the specified secondary endpoints of performance evaluation (such as sensitivity and specificity) per protocol. This included estimates of performance parameters including meta-analysis results of ^{68}Ga-DOTATATE pooled sensitivity and pooled specificity of available qualifying published papers. The standard of truth used in the classification of true positive/ negative and false positive/negative, for all included studies, was based upon a composite of conventional imaging (CT/MRI), clinical information, and/or histopathology.

The articles attempted to address changes in management but the information in the articles was lacking sufficient detail. Due to the lack of publication reporting relevant data for ^{68}Ga-DOTATATE compared to ^{111}In-pentetreotide, and the heterogeneity in the methodology used to assess the change in patient management, formal meta-analysis per protocol was not conducted on change in patient management.

There were three comparative studies. There was one published article - prospective, non-randomized, single center, open-label, comparative study conducted at the Vanderbilt University Medical Center (VUMC). There were 2 other articles that were retrospective and blinded that compared to OctreoScan with conventional imaging (CI) as the Standard of Truth (SOT). Other articles were retrospective and unblinded. The patient populations were metastatic, suspected recurrence, post-operative and few primary presentations.

For the prospective VUMC study, a total number of 97 adult patients with known or suspected neuroendocrine tumors (mean age 54±11; 58% female; 68% of primary tumor localized in the gastroenteropancreatic area, 12% of unknown primary localization, and remaining 20% were hindgut or rectum or pulmonary or symptoms only were enrolled. ^{111}In-pentetreotide scan type for all 97 patients included planar (5%), SPECT (31%), SPECT/CT (52%) and missing (12%). All 97 patients received one injection of ^{68}Ga-DOTATATE on the day of the medical imaging. Average Activity administered was 5.3 mCi (SD 0.3, range 4.3 to 6.0 mCi) and average time between administration and image acquisition was 65 minutes (range 55 to 93 minutes). Median (Quartiles) number of days between ^{111}In-pentetreotide and ^{68}Ga-DOTATATE scans was 176 (105; 354).

There were 78 evaluable patients with comparable scans in this study. The standard of truth was a composite of previous conventional imaging (CT and/or MRI) and histopathology assessment of resected specimen. All investigational scans were read by at least two experienced board-certified nuclear medicine physicians (blinded to the patient's identity and to any other clinical information prior to initial interpretation.) Discrepancies were resolved by consensus of the two interpreting physicians or, in event of failure to reconcile, by a third physician.

When directly comparing the imaging performance of these two products, the sensitivity for ^{68}Ga-DOTATATE was statistically significantly superior to ^{111}In-pentetreotide (96% [95% CI: 86, 100] vs. 72% [58, 84]; McNemar's chi^2, p = 0.003). This difference was mainly explained by the lower number of false negative for ^{68}Ga-DOTATATE (2 cases) compared to ^{111}In-pentetreotide (14 cases). However, the difference observed in the specificity was not statistically significant (93% [77, 99] for ^{68}Ga-DOTATATE vs. 89% [72, 98] for ^{111}In-pentetreotide; McNemar's chi^2, p = 1.000).

A total of 13 studies met all the inclusion criteria for inclusion for the Meta-analysis. Out of these 13 studies 9 qualified for pooled sensitivity estimation based on meta-analysis and 5 qualified for pooled specificity. The pooled sensitivity based on meta-analysis for ^{68}GaDOTATE was 90% with 95% CI (86 – 100%) and for 5 qualified studies, the pooled specificity was 90% with 95% CI (84% - 95%). The details are given in the following Table 1.

Table 1: Sensitivity & Specificity patient-based estimates for ^{68}Ga-DOTATATE All Studies

Author/Year[1]	Design [2]	# Patients	# TP+FN	# TP (detected)	Patient-Based Sensitivity (%) 95% CI	# TN+FP	# TN (detected)	Patient-Based Specificity (%) 95% CI
Comparative Studies								
VUMC 1990	P	78	50	48	96 (86-100)	26	3	93 (76 – 99)
Srirajaskanthan 2010	R	51	47	41	87 (74-95)	4	4	100 (40 – 100)
Hofman 2012	R	59	52	0	100 (93 – 100)	7	6	86 (42 – 100)
Non-comparative Studies								
Alonso 2014	R	29	29	23	79 (6- - 92)	NA	NA	NA
Haug 2014	R	45	18	17	94 (73 – 100)	27	24	89 (71 – 98)
Haug 2012	R	104	36	29	81 (64 – 92)	68	61	90 (80 – 96)
Haug 2009	R	25	25	24	96 (80 -100)	NA	NA	NA
Kayani 2008	R	38	38	31	82 (66-92)	NA	NA	NA
Wild 2013	R	18	18	17	94 (73 - 100)	NA	NA	NA
Meta-Analysis All Studies					90 (86 - 93)			90 (76 – 99)

[1]First author & Year of Publication

[2]Design: P = Prospective R = Retrospective NA = Not Available

Note: VUMC represents an ongoing academic study, with preliminary unpublished results included in the above.

2. INTRODUCTION

^{68}Ga-DOTATATE is a radiopharmaceutical product used for functional imaging with positron emission tomography (PET) when the increased expression of somatostatin receptor (SSTR) is a diagnostic target. Several types of tumors are known to significantly express SSTR and therefore the density of SSTR expression may be visualized with ^{68}Ga-DOTATATE.

(b) (4) is supplied as a sterile, single use kit for preparing a monodose radiopharmaceutical gallium-68 (^{68}Ga) DOTA^{0}-Tyr^{3}-Octreotate. The Drug substance is prepared in a radiopharmacy facility using a kit which has been developed by Advanced Accelerator Applications. The kit contains components that are assembled on the day of use, including the two drug substance precursors: DOTATATE, and Gallium-68.

This medicinal product is for diagnostic use only.

Clinical trials sponsored by the Applicant with (b) (4) as an investigational medicinal product were not planned.

2.1 Overview

^{111}In-pentetreotide, an analog of the hormone somatostatin (SST), was granted a marketing authorization in the US and most European Union (EU) countries under the name Octreoscan® for in vivo scintigraphic imaging of the biodistribution of SSTR more than 20 years ago. Also, the positron emission tomography (PET) had been introduced as the most modern and the most sensitive imaging method of nuclear medicine. PET with ^{68}Ga-DOTA-conjugated SST analogs brought improvements in spatial resolution of functional SSTR imaging.

The sponsor states that the clinical safety and efficacy of ^{68}Ga-DOTATATE has been characterized over the past decade of clinical use (b) (4) The first data on the use of Ga-DOTATATE for somatostatin receptor PET (SRPET) in a series of patients were published in 2008 (Kayani et al, 2008). ^{68}Ga- DOTATATE has been used in the USA for more than 10 years, mainly in the diagnostic imaging of neuroendocrine tumors.

The sponsor submitted a 505(b)(2) NDA based on a survey of abstracts of recent scientific and medical literature conducted to identify areas of current interest in ^{68}Ga-DOTATATE from a clinical perspective. The search was conducted on PubMed, a service of the US National Library of Medicine. This included the Medline and Toxline core databases. The relevant publications were subsequently retrieved and analyzed.

This search resulted in 211 articles, of which 76 articles were clinical in nature. Studies relating to ^{68}Ga-DOTATATE efficacy and mechanism of action accounted for 26 publications. Studies relating to ^{68}Ga-DOTATATE safety accounted for 8 publications. The studies in this category relate generally to well-documented clinical toxicities of ^{68}Ga-DOTATATE. None of studies were performed by Sponsor.

2.1.1 Regulatory History

Advanced Accelerator Applications (AAA) submitted a 505(b)(2) NDA for [redacted] (Kit for the preparation of ^{68}Ga-DOTAT ATE for injection) on July 1, 2015. The timeline for the regulatory history is as flows:

- 12/2013 The sponsor stated that the FDA granted orphan drug status for ^{68}Ga-DOTATATE in December 2013 (designation 13-4136) as a diagnostic for [redacted] neuroendocrine tumors ([redacted] NETs). This orphan product is intended to diagnose a serious and life-threatening disease. There is a critical unmet medical need that is widely recognized in the medical community and among regulatory authorities. (Note: An email from Orphan Drug says that the orphan # is 15/4839 for AAA. AAA has orphan designation [redacted])
- 7/1/14: DMIP agreed to a literature based NDA (IND 122818) supported by the results of the expanded access pivotal study conducted at Vanderbilt University Medical Center (VUMC) in a pre-IND meeeting.
- 11/19/14: DMIP provided advice on the methodology of the systematic review, toxicity scale, endpoints, and the Statistical Analysis Plan (SAP).
- 1/9/15: Sponsor submitted a SAP. As DMIP was sending comments, the sponsor submitted the NDA on 7/1/15.
- 8/26/2017 Clinical and Statistical Information Request was sent to the sponsor.
- 10/7/2015 Another major Clinical and Statistical Information Request was sent to the sponsor.

Safety and efficacy data presented in this NDA relies on published literature and one prospective study (VUMC). No randomized, prospective trials with blinded review were designed for drug development or identified in the literature search. Population is variable among the articles. No clinical studies were conducted by AAA. The sponsor stated that AAA has access to reference data from Vanderbilt University Medical Center pivotal study.

2.1.2 Doses

[redacted]® is supplied as a single-use monodose kit, containing two vials and an accessory cartridge, which allows for direct preparation of ^{68}Ga-DOTATATE (^{68}Ga-DOTA0-Tyr3 -0ctreotate) with a ^{68}GaCl3 solution provided by a ^{68}Ge/68Ga generator which meets the required pharmaceutical quality standards, avoiding any additional steps of eluate processing and product purification. After reconstitution, the ^{68}Ga-DOTATATE solution is administered intravenously, therefore immediately and completely bioavailable.

After reconstitution and radiolabelling with activities of up to 1110 MBq (30 mCi), the ^{68}Ga-DOTATATE solution must be stored upright with an appropriate shielding to protect from radiation, at a temperature below 77°F (+25 °C), and for a maximum of 4 hours.

The recommended radioactivity to be administered for positron emission tomography (PET) imaging in adults is 2 MBq/kg of body weight (0.054 mCi/kg), (b) (4) and not more than 200 MBq (5.4 mCi). The final radioactivity to be administered depends on the characteristics of the PET camera and should comply with the Diagnostic Reference Levels (DRL) and regulation requirements.

2.1.3 Identified Studies in the review

This application is based on overview of available literature data supported by a meta-analysis of published results of clinical studies with ^{68}Ga-DOTATATE in a series of patients, and by efficacy and safety data of ^{68}Ga-DOTATATE from a clinical study conducted at the Vanderbilt University Medical Center (VUMC). a prospective study

Statistical Review has focused on the groups of following literature based studies.

- A prospective, non-randomized, single center, open-label comparative study conducted at the Vanderbilt University Medical Center (VUMC): "^{68}Ga-DOTATATE PET Scan in Neuroendocrine Cancer," The objective of this trial was to compare ^{68}Ga-Dotatate PET scan imaging to the existing standard-of-care somatostatin receptor imaging agent, ^{111}In-octreotide, and also to test for non-inferiority to multi-modality conventional imaging. The Applicant was granted access to the results of this study.

- Comparative studies - retroactive summary data from literature based studies comparing technical performance of ^{68}Ga-DOTATATE to ^{111}In-pentetreotide for defined criteria.

- Non-comparative studies in patients with suspected NETs due to clinical symptoms, elevated levels of tumor markers, or indeterminate tumors suggestive of NET.

- Meta-Analysis for the performance characteristic of ^{68}Ga-DOTATATE

2.1.4 Analysis Populations

The analysis was limited to the summary information available from the reported summary data included in qualified literature review articles and a prospective non-randomized, single center, open-label, comparative study conducted at the Vanderbilt University Medical Center (VUMC).

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for the publication of systematic reviews and meta-analyses. The electronic search returned 2,378 articles, with one additional article added from bibliography reviews, giving a total of 2,379 study abstracts screened. After the initial abstract review, 2,344 articles were excluded. Thirty-five studies received a full review, of which 22 were excluded upon closer analysis. The remaining 13 studies met all the inclusion criteria and were used for the final analysis. Analysis population & study characteristics are given in Table 2.

Table 2: Analysis Population - Study Characteristics (Sponsor)

Study Country	Number of patients	Study type	Blinding	Patient Population
Studies comparing ^{68}Ga-DOTATATE to ^{111}In-DTPA-Octreotide				
Srirajaskanthan 2010 UK	51	Retrospective	Blinded	Chosen after negative or equivocal ^{111}In-DTPA-Octreotide scan.
Hofman 2012 Australia	59	Retrospective	Blinded	Based on clinical need. 52 proven or suspected GEP or bronchial NETs and 7 neural crest/ mesenchymal tumors.
VUMC 2015 (access as per data use agreement)	97	Prospective	Blinded	97 consecutive patients with known or suspected pulmonary or GEP NETs.
Studies comparing ^{68}Ga-DOTATATE to conventional imaging				
Kayani 2008 UK	38	Retrospective	Not reported	Finding of metastatic disease in 28 GEP, 6 lung, and 4 metastatic NETs with confirmed primary or recurrent disease.
Haug 2009 Germany	25	Retrospective	Unblinded	Metastatic disease in 14 GEP, 6 lung, 4 unknown primary, and 1 paranasal sinus.
Haug 2012 Germany	104	Retrospective	Unblinded	Patients with clinical suspicion of NET, elevated blood levels of tumor markers and image-based suspicion of NET. Presence of NET validated by histopathology.
Poeppel 2013 Germany	27	Retrospective	Blinded	All histologically verified GEP tumors with and without recurrence.
Wild 2013 UK	18	Retrospective	Blinded	Biopsy-proven metastatic GEP with CT or MRI imaging also available from long-term surveillance.
Alonso 2014 Uruguay	29	Retrospective	Not reported	Pathologically proven neuroendocrine metastases but unknown primary origin.
Etchebehere 2014 Brazil	19	Retrospective	Blinded	Patients with histologically determined NETs with suspected recurrence.
Haug 2014 Germany	45	Retrospective	Blinded	History of curative resection of NET.
Studies included for safety evaluation only				
Lapinska 2011 Poland	97	Retrospective	Not reported	Patients with confirmed or suspected NET.
Brogsitter 2013 Germany	23	Retrospective	Blinded	Patients with known somatostatin receptor-positive metastases from NETs, thyroid cancer or glomus tumors.
Ilhan 2015 Germany	44	Retrospective	Blinded	Patients suffering NET of the ileum or pancreas.

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2.2 Data Sources

Data elements of interest were extracted from the studies that met inclusion/exclusion criteria. Variables of interest included study author (reported by name of the first author), title of the publication, year of publication, number of patients, number of males, number of females, mean age, etc..

The outcome measures of interest were reported at patient-level. In this report, the information related to sensitivity and specificity are reported. Data were only provided for VUMC study in SAS format.

The NDA in eCTD and SAS export files of these data are located at:
Location: \\CDSESUB1\evsprod\NDA208547\208547.enx

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There were several information requests sent to the sponsor to clarify several analyses in the primary analysis section of the NDA and analyses related to the secondary endpoints.

The sponsor responded that the primary analysis as per meta-analysis protocol and SAP should have been the direct comparison of ^{68}Ga-DOTATATE and Octreoscan based on testing for non-inferiority of the two summary receiver operator characteristic (SROC) areas by a one sided chi-square test. However, the number of publications fulfilling the inclusion/exclusion criteria of the literature review was limited. This resulted in the lack of exploitable data for a direct comparison of the two imaging methods. Due to the lack of adequate published data, a direct comparison of ^{68}Ga- DOTATATE and ^{111}In-pentetreotide (primary analysis planned in the meta-analysis protocol and Statistical Analysis Plan (SAP)) was not possible. Therefore, the selection of a non-inferiority margin was not necessary. (Note: this was not communicated to the agency any time prior to information request by the Agency). The sponsor had submitted SAP, Agency reviewed it but before the Agency could send the comments to the sponsor, the NDA was submitted. The primary analysis per protocol or per Statistical Analysis Plan (SAP) submitted to the Agency was not conducted.

In an Information request DMIP recommended evaluating the performance (sensitivity and specificity) of the ^{68}Ga-DOTATATE with respect to well defined standard of truth as the primary endpoint. The sponsor stated that the primary analysis planned in the protocol and SAP was not possible. Therefore, the sponsor focused on the specified secondary endpoints of performance evaluation (such as sensitivity and specificity) per protocol. This included estimates of performance parameters including meta-analysis results of ^{68}Ga-DOTATATE pooled sensitivity and pooled specificity of available qualifying published papers. The standard of truth used in the classification of true positive/ negative and false positive/negative, for all included studies, was based upon a composite of conventional imaging (CT/MRI), clinical information, and/or histopathology.

Patient level data were provided only for VUMC study SAS (xpt) format. Since the data were captured from the published articles and reports, the quality of data, was limited to the published information. The population is variable among the articles.

The articles attempted to address changes in management but the information in the articles was lacking sufficient detail. Due to the lack of publication reporting relevant data for ^{68}Ga-DOTATATE compared to ^{111}In-pentetreotide, and the heterogeneity in the methodology used to assess the change in patient management, formal meta-analysis for changes in patient management per protocol was not conducted.

Reference ID: 3860199

3.2 Evaluation of Efficacy

3.2.1 Study Design

This was a 505(b)(2) NDA submission based on a survey of abstracts of recent scientific and medical literature conducted to identify areas of current interest in ^{68}Ga-DOTATATE from a clinical perspective. The search was conducted on PubMed, a service of the US National Library of Medicine. This included the Medline and Toxline core databases. The relevant publications were subsequently retrieved and analyzed.

3.2.2 Objective

The objectives were to perform a systematic review and, if sufficient data were available, to conduct a meta-analysis to assess the imaging performance, impact on disease management, and safety of ^{68}Ga-DOTATATE PET/CT in patient with pulmonary or (b) (4) NETs overexpressing somatostatin receptors, compared to ^{111}In-DTPA-Octreotide imaging. The primary endpoint was the difference in imaging performance between ^{68}Ga-DOTATATE PET/CT to ^{111}In-DTPA-Octreotide SPECT imaging performance, as assessed by summary receiver operator characteristic (SROC) curves. The hypothesis was that ^{68}Ga-DOTATATE was considered effective if its imaging performance was non-inferior to that of the current image standard ^{111}In-DTPA-Octreotide. In addition to the primary endpoint, the secondary endpoint was to demonstrate the non-inferiority of ^{68}Ga-DOTATATE PET/CT compared to ^{111}In-DTPA-Octreotide SPECT for changes in patient management

3.2.3 Protocol Defined Methods of Analysis

The protocol and SAP defined method of analysis was direct comparison of ^{68}Ga-DOTATATE and Octreoscan based on testing for non-inferiority of the two summary receiver operator characteristic (SROC) areas by a one sided chi-square test. However, the number of publications fulfilling the inclusion/exclusion criteria of the literature review was limited. This resulted in the lack of exploitable data for a direct comparison of the two imaging methods. Thus the primary analysis as planned was not possible to conduct. Due to the lack of adequate published data, a direct comparison of ^{68}Ga- DOTATATE and ^{111}In-pentetreotide (primary analysis planned in the meta-analysis protocol and Statistical Analysis Plan (SAP)) was not possible. Therefore, the selection of a non-inferiority margin was not necessary. (Note: this was not communicated to the agency any time prior to information request by the Agency). The sponsor submitted SAP, Agency reviewed it but before the Agency could send the comments to the sponsor, the NDA was submitted.

3.2.4 Demographic and Baseline Characteristics

Due to the nature of data presented in the reported study publications in the analysis population, limited information on demographic and baseline characteristics were available. Table 4 provides baseline characteristics available studies in this submission. The available baseline characteristics are given in the following Table 3:

Reference ID: 3860199

Table 3: Baseline Characteristics

Study	Age (mean)	% Male	Imaging procedure	Time after injection (min)	Standard of Truth (SOT)
Studies comparing ^{68}Ga-DOTATATE to ^{111}In-DTPA-Octreotide					
**Srirajaskanthan 2010 (n=51)	55	53	PET/CT static acquisition with visual interpretation	60	Histology and/or clinical/imaging follow-up
**Hofman 2012 n=59	50	36	PET/CT static acquisition with visual and semi-quantitative interpretation	30 - 60	Histology and/or imaging follow-up
**VUMC 2015 n=91, eval 78	53	42	PET/CT static with visual interpretation	55 - 93	Histology and/or clinical/imaging follow-up
Studies comparing ^{68}Ga-DOTATATE to conventional imaging					
*Kayani 2008 (n = 38)	53	66	PET/CT static acquisition with visual and semi-quantitative interpretation	45 - 60	Histology and/or imaging follow-up
*Haug 2009 (n = 33)	57	64	PET/CT static acquisition with visual and semi-quantitative interpretation	60	Histology and/or clinical/imaging follow-up
**Haug 2012 n = 53	58	50	PET/CT static acquisition with visual interpretation	60	Histology and/or imaging/clinical follow-up
Poeppel 2013 (n = 27)	62	78	PET/CT; NR; visual interpretation	24-161	NA
*Wild 2013 n=18	58	56	PET/CT static acquisition with visual and semi-quantitative interpretation	54 -73	Histology and/or imaging follow-up
Alonso 2014 (n = 29)	60	41	PET/CT; NR; visual and semi-quantitative interpretation	30	Histology and/or clinical/imaging follow-up
Etchebehere 2014 (n=19)	54	53	PET/CT static acquisition with visual interpretation	45	Histology and/or patient follow-up
**Haug 2014 n=63	58	54	PET/CT static acquisition with visual interpretation	60	Histology and/or clinical/imaging follow-up
Studies included for safety evaluation only					
Lapinska 2011	54	41	PET/CT static acquisition with visual and semi-quantitative interpretation	45-60	NA
Brogsitter2014	62	74	PET/CT; NR; visual interpretation	33 – 73	Combination of the two imaging modalities (investigational and comparator)
Ilhan 2014	56	55	PET/CT static acquisition with visual interpretation	60	Histology

* Studies identified for sensitivity evaluation in Meta-Analysis
** Studies identified for both sensitivity & specificity evaluation in Meta-Analysis

Reference ID: 3860199

3.3 Results and Conclusions

There were three comparative studies. Efficacy evaluation for each of these three studies is given below:

3.3.1 Study 1 - Vanderbilt University Medical Center (VUMC) pivotal study

Design: A prospective, non-randomized, single center, open-label study comparing ^{68}Ga-DOTATATE with conventional imaging including ^{111}In-pentreotide in Phase I/II diagnostic performance study.

The study was not designed to be a clinical trial for drug development.

Primary Objective – Efficacy and Safety Assessment

Secondary Objective - Demonstrate impact on care that results from adding ^{68}Ga-DOTATATE PET/CT to current standard of care imaging

Efficacy Assessments:

A total number of 97 adult patients with known or suspected neuroendocrine tumors (mean age 54±11; 58% female; 68% of primary tumor localized in the gastroenteropancreatic area, 12% of unknown primary localization, and remaining 20% were hindgut or rectum or pulmonary or symptoms only were enrolled. ^{111}In-pentetreotide scan type for all 97 patients included planar (5%), SPECT (31%), SPECT/CT (52%) and missing (12%). All 97 patients received one injection of ^{68}Ga-DOTATATE on the day of the medical imaging. Average Activity administered was 5.3 mCi (SD 0.3, range 4.3 to 6.0 mCi) and average time between administration and image acquisition was 65 minutes (range 55 to 93 minutes). Median (Quartiles) number of days between ^{111}In-pentetreotide and ^{68}Ga-DOTATATE scans was 176 (105; 354).

There were 78 evaluable patients with comparable scans (10 had no Pentetreotide scan, 5 had no post-surgical Pentetreotide, and time between scans was > 3 years for 4 patients). The tumor location in these 78 patients were bowel (37), gastric (18), CUP (7), symptoms only(7), pulmonary(5), hindgut(3) and other(1). The standard of truth was a composite of previous conventional imaging (CT and/or MRI) and histopathology assessment of resected specimen.

All investigational scans were read by at least two experienced board-certified nuclear medicine physicians (blinded to the patient's identity and to any other clinical information prior to initial interpretation.).

Discrepancies were resolved by consensus of the two interpreting physicians or, in event of failure to reconcile, by a third (unblinded) physician.

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Discrepancies were recorded for statistical analysis, with final resolution (e.g. consensus vs. third party intervention). Disagreement by all three was possible and was also noted.

The final report was then provided for clinical management, but any controversies were clearly communicated to the clinical care givers and to statisticians for data analysis.

Primary Analysis

Full Analysis Set (FAS); n = 78 patients

The standard of truth used in the classification of true positive/negative and false positive/negative, for all included studies, was based upon a composite of conventional imaging (CT/MRI), clinical information, and/or histopathology.

The results are given in the following Table 4 and Table 5

Table 4: Sensitivity Analysis of VUMC stury

	Reference Standard		
^{68}Ga-DOTATATE	**Cancer**	**Benign**	**Total**
Cancer	**48**	**2**	**50**
Benign/NED	**2**	**26**	**28**
Total	**50**	**28**	**78**

Table 5: Specificity Analysis of VUMC Study

	Reference Standard		
^{111}In-pentetreotide	**Cancer**	**Benign**	**Total**
Cancer	**36**	**3**	**39**
Benign/NED	**14**	**25**	**39**
Total	**50**	**28**	**78**

Results:

Sensitivity for ^{68}Ga-DOTATATE = 48/50 = 96%; 95% CI (86.3, 99.5%)
Sensitivity for ^{111}In-pentetreotide = 36/50 = 72%; 95% CI (57.5, 83.8%)

Specificity for ^{68}Ga-DOTATATE = 26/28 = 93%; 95% CI (76.5, 99.1%)
Specificity for ^{111}In-pentetreotide = 25/28 = 89%; 95% CI (71.8, 97.7%)

When directly comparing the imaging performance of these two products, the sensitivity for ^{68}Ga-DOTATATE was statistically significantly superior to ^{111}In-pentetreotide (96% [95% CI: 86, 100] vs. 72% [58, 84]; McNemar's chi^2, p = 0.003). This difference was mainly explained by the lower number of false negative for ^{68}Ga-DOTATATE (2 cases) compared to ^{111}In-pentetreotide (14 cases). However, the difference observed in the specificity was not statistically significant (93% [77, 99] for ^{68}Ga-DOTATATE vs. 89% [72, 98] for ^{111}In-pentetreotide; McNemar's chi^2, p = 1.000).

Study 1: Patient Management Impact:

(b) (4)

(b) (4). Ga-DOTATATE demonstrated 12 patients as non-surgical candidates, with strong uptake to support peptide receptor radionuclide therapy. In contrast, 3 of these 12 (25%) patients were miss-classified by ^{111}In-pentetreotide.

3.3.2 Study 2 - Srirajaskanthan et al, 2010

Title: "The **role of** ^{68}Ga-DOTATATE PET in Patients with Neuroendocrine Tumors and Negative or Equivocal Findings on ^{111}In-DTPA-Octreotide Scintigraphy"

Prospective enrollment; Retrospective evaluation

Selected group of adult patients with negative or weakly positive findings on ^{111}In-pentetreotide scintigraphy

Objective: to determine whether ^{68}Ga-DOTATATE PET/CT is able to detect additional disease and, if so, whether patient management is modified

Standard of Truth: CI (Biology, imaging. Follow-up), Methods of comparison not specified

A subset of NET population

N=51 – histologically confirmed NET–all had undergone scanning with ^{111}In-DTPA-octreotide
47 had evidence of disease on cross-sectional imaging or biochemically.

Sensitivity (patient based) = 41/47 = 87.2% (Patient Based Detection Rate) [TP = 41 & FN = 6]
95% CI (74 – 95)

Specificity (patient based) = 100%
95% CI (39.8, 100.0) [TN = 4 & FP = 0]

A total of 226 lesions were identified on cross-sectional imaging

Sensitivity (lesion based) 168/226=74.3% (Lesion Based Detection Rate)
95% CI (68.1, 79.9)

DOTATATE identified more lesions than ^{111}In-pentetreotide scintigraphy

Sensitivity of DTPA-Octreotide was not determined
One false positive was identified with DTPA-Octreotide –
Specificity of DTPA-Octreotide = 98%

Study 2: Patient Management Impact:

DOTATATE imaging changed scheduled management in 36/51=70.6% patients, who were subsequently deemed suitable for peptide receptor-targeted therapy .

3.3.3 Study 3 - Michael S Hofman (2012) et al. (Melbourne, Australia):

No Standard of Truth Mentioned – No diagnostic performance measures

N = 59 GaTate PET/CT performed over an 18 month period
52 proven or suspected gastro-entero-pancreatic (GEP) or bronchial neuroendocrine tumors
4 Phaeochromocytoma
3 Others
40 had both scan modalities

Sensitivity = 100% -- CI (93.2, 100.0) TP = 52 FN = 0
Specificity = 86% -- CI (93.2, 100.0) TN = 6 FP = 1

Study 2: Patient Management Impact:

^{68}Ga-DOTATATE provided additional information in 83% of patients compared with In-111 octreotide imaging, and in 68% of patients compared with conventional imaging. Bone metastasis (18 patients) was the most common differential result. Management impact included directing patients to curative surgery, by identifying a primary site and directing patients with multiple metastases to systematic therapy.

3.3.4 Summary of the performance of comparative studies

In comparative studies, ^{68}Ga-DOTATATE showed better performance than ^{111}In-pentetereotide. The following Table 6 summarizes performance estimates for ^{68}Ga-DOTATATE for 3 comparative studies in this submission.

Table 6: Sensitivity & Specificity patient-based estimates for ^{68}Ga-DOTATATE comparative studies

Author/Year[1]	Design [2]	# Patients	# TP+FN	# TP (detected)	Patient-Based Sensitivity (%) 95% CI	# TN+FP	# TN (detected)	Patient-Based Specificity (%) 95% CI
VUMC 1990	P	78	50	48	96 (86-100)	26	3	93 (76 – 99)
Srirajaskanthan 2010	R	51	47	41	87 (74-95)	4	4	100 (40 – 100)
Hofman 2012	R	59	52	52	100 (93 – 100)	7	6	86 (42 – 100)

[1]First author & Year of Publication

[2]Design: P = Prospective R = Retrospective NA = Not Available

Note: VUMC represents an ongoing academic study, with preliminary unpublished results included in the above.

3.3.5 Non-comparative supportive studies

A few non-comparative studies are described here

2013 Wild

N=18 NET with CI as SOT
Patient-Based Sensitivity = 95% (17/18)

2014 Haug

Retrospective, single center, consecutive, post-resection, N=63, consensus read included n=30, routine, n=33 suspicion of recurrence, Readers were unblinded to clinical history and re-read blinded (different readers)

The following Table 7 summarizes the performance characteristics of Haug Study

Table 7: Sensitivity and Specificity of 2014 Haug Study Total n=63

	All Patients n= 63			Suspected Recurrence n=33			Surveillance n = 30			GEP NETS n = 45		
	Un-bl	BR1	BR2	Un-bl	BR1	BR2	Un-bl	BR1	BR2	Un-bl	BR1	BR2
Sensitivity (%)	90	79	76	90	81	85	87	75	50	94	83	89
Specificity (%)	82	85	94	58	75	92	95	91	95	89	85	93

Un-bl = Un-blinded Reader; BR1 = Blinded Reader 1; BR2 = Blinded Reader 2

Reference ID: 3860199

2014 Haug - Change in management included surgical resection 11 cases, chemotherapy 6 cases, PRRT 5 cases, somatostatin analogs 3 cases and local treatment of liver metastases 1 case. Details of management decisions were not available

Limitation - The exact methodology for image interpretation and change in management are not specified

3.3.6 Summary of the performance of non-comparative studies

Table 8 summarizes performance estimates for ^{68}Ga-DOTATATE for 6 non-comparative studies in this submission.

Table 8: Sensitivity & Specificity patient-based estimates for ^{68}Ga-DOTATATE non-comparative studies

Author/Year[1]	Design [2]	# Patients	# TP+FN	# TP (detected)	Patient-Based Sensitivity (%) 95% CI	# TN+FP	# TN (detected)	Patient-Based Specificity (%) 95% CI
Alonso 2014	R	29	29	23	79 (6- - 92)	NA	NA	NA
Haug 2014	R	45	18	17	94 (73 – 100)	27	24	89 (71 – 98)
Haug 2012	R	104	36	29	81 (64 – 92)	68	61	90 (80 – 96)
Haug 2009	R	25	25	24	96 (80 -100)	NA	NA	NA
Kayani 2008	R	38	38	31	82 (66-92)	NA	NA	NA
Wild 2013	R	18	18	17	94 (73 – 100)	NA	NA	NA

[1]First author & Year of Publication

[2]Design: P = Prospective R = Retrospective NA = Not Available

3.3.7 Meta-Analysis

The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for the publication of systematic reviews and meta-analyses. The electronic search returned 2,378 articles, with one additional article added from bibliography reviews, giving a total of 2,379 study abstracts screened. After the initial abstract review, 2,344 articles were excluded. Thirty-five studies received a full review, of which 22 were excluded upon closer analysis. The remaining 13 studies met all the inclusion criteria. Results for estimating the performance characteristics of ^{68}Ga-DOTATATE for each study are summarized in the Table 9. These studies varied widely in underlying patient populations and purposes of the study.

Table 9: ^{68}Ga-DOTATATE Efficacy Results – (Sponsor)

Study	Cancer/Benign	Sensitivity (%)	Specificity (%)	Treatment Management
Studies comparing ^{68}Ga-DOTATATE to ^{111}In-DTPA-Octreotide				
Hofman 2012	52/7 (40 had both scan modalities)	100 TP 52 FN 0	86 TN 6 FP 1	^{68}Ga-DOTATATE provided additional clinically significant information in 83% of patients. Bone metastasis (18 patients) was the most common differential result.
Srirajaskanthan 2010	47/4	87 TP 41 FN 6	100 TN 4 FP 0	Major impact on 71% of patients, with PRRT (N=20) treatment being the most common change.
VUMC 2015 (access as per data use agreement	50/28	96 TP 48 FN 2	93 TN 26 FP 2	Clinical care beneficial impact on 38% of patients.
Studies comparing ^{68}Ga-DOTATATE to conventional imaging				
Alonso 2014	29/0	79 TP 23 FN 6	Not applicable	^{68}Ga-DOTATATE detected previously unknown tumors in 59% of patients. Pathology was confirmed in 24% who underwent surgery.
Etchebehere 2014	N=19 (results reported by region not by patient)	96[a]	97[a]	^{68}Ga-DOTATATE found bone metastases missed by weighted MRI and SPECT/CT.
Haug 2014	18/27	94 TP 17 FN 1	89 TN 24 FP 3	^{68}Ga-DOTATATE was accurate for the detection of recurrent NET following curative resection.
Haug 2012	36/68[b]	81 TP 29 FN 7	90 TN 61 FP 7	^{68}Ga-DOTATATE findings contributed to patient management decisions via localization or exclusion of a present NET.
Haug 2009	25/0	96 TP 24 FN 1	Not applicable	Superior sensitivity to ^{18}F-DOPA, other changes to treatment not stated when compared to conventional imaging.
Kayani 2008	38/0	82 TP 31 FN 7	Not applicable	All metastatic disease determined by pathology. Change in PRRT therapy in 4 patients with low DOTATATE uptake.
Poeppel 2013	40/0	Not reported	Not applicable	No difference in the two methods of detection. No change in PRRT based upon either modality. No comment on etiology or number of false positive or false negative foci of uptake.
Wild 2013	18/0	94 TP 17 FN 1	Not applicable	No difference in the two methods of detection. Metastatic disease found by conventional imaging was missed by DOTATATE. Change in treatment in 3 patients (surgical extent).

[a] for all solid organs, Sensitivity 100% and specificity 100% for musculoskeletal and liver metastases.
[b] included 12 patients who did not have a NET tumor
TP = true positive; FN = false negative; TN = true negative; FP = false positive

Reference ID: 3860199

Thirteen (13) studies met all the inclusion criteria for inclusion for the Meta-analysis. Out of these 13 studies 9 qualified for pooled sensitivity estimation based on meta-analysis and 5 qualified for pooled specificity. The pooled sensitivity based on meta-analysis for ^{68}GaDOTATE was 90% with 95% CI (86 – 100%) and for 5 qualified studies, the pooled specificity was 90% with 95% CI (84% - 95%). The details are given in the following Table 10. Forest plots are also provided.

Table 10: Sensitivity & Specificity patient-based estimates for ^{68}Ga-DOTATATE All Studies

Author/Year[1]	Design [2]	# Patients	# TP+FN	# TP (detected)	Patient-Based Sensitivity (%) 95% CI	# TN+FP	# TN (detected)	Patient-Based Specificity (%) 95% CI
Comparative Studies								
VUMC 1990	P	78	50	48	96 (86-100)	26	3	93 (76 – 99)
Srirajaskanthan 2010	R	51	47	41	87 (74-95)	4	4	100 (40 – 100)
Hofman 2012	R	59	52	0	100 (93 – 100)	7	6	86 (42 – 100)
Non-comparative Studies								
Alonso 2014	R	29	29	23	79 (6- - 92)	NA	NA	NA
Haug 2014	R	45	18	17	94 (73 – 100)	27	24	89 (71 – 98)
Haug 2012	R	104	36	29	81 (64 – 92)	68	61	90 (80 – 96)
Haug 2009	R	25	25	24	96 (80 -100)	NA	NA	NA
Kayani 2008	R	38	38	31	82 (66-92)	NA	NA	NA
Wild 2013	R	18	18	17	94 (73 - 100)	NA	NA	NA
Meta-Analysis All Studies					90 (86 - 93)			90 (76 – 99)

[1]First author & Year of Publication

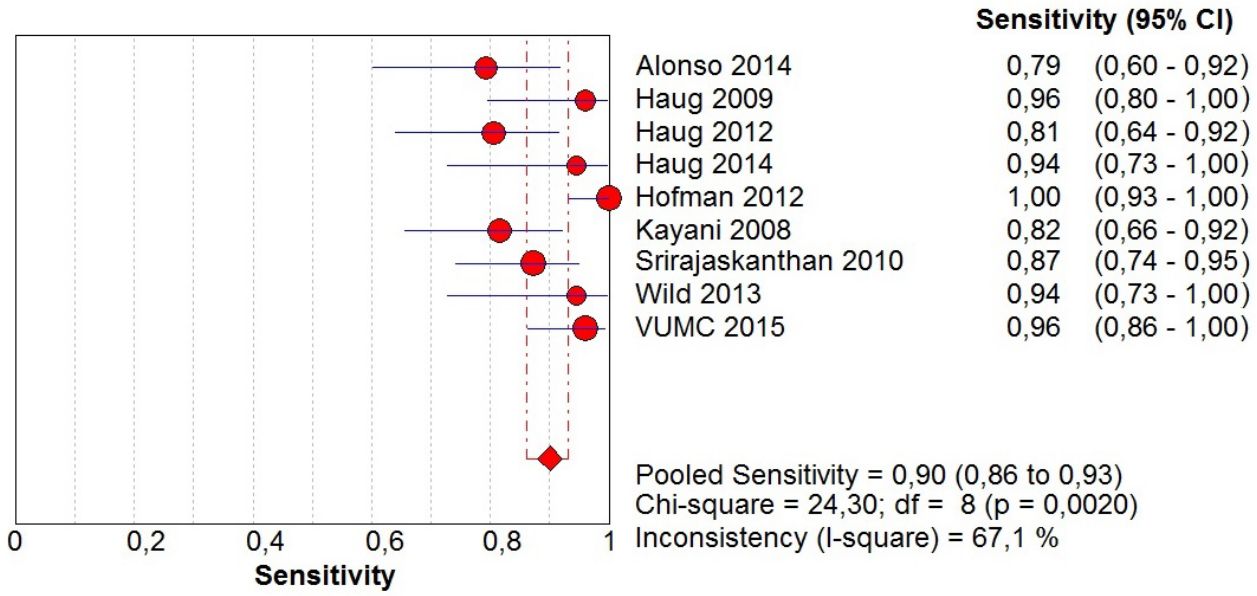
[2]Design: P = Prospective R = Retrospective NA = Not Available

Note: VUMC represents an ongoing academic study, with preliminary unpublished results included in the above.

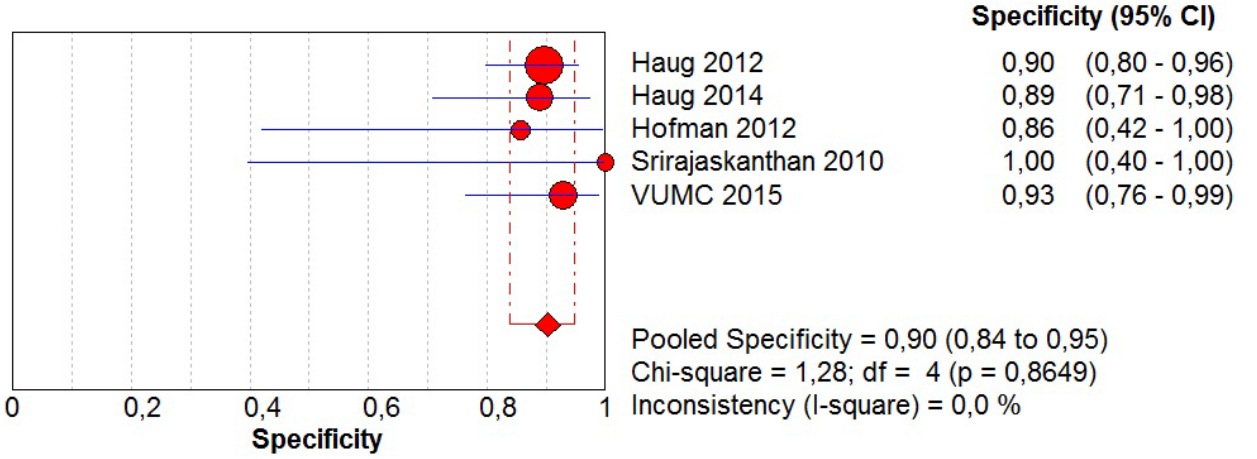
Reference ID: 3860199

3.3.7 Forest Plots

Forest Plots with Random Effects Estimates and Individual Study Sensitivity for ^{68}Ga-DOTATATE (Sponsor)



Forest Plots with Random Effects Estimates and Individual Study Specificity for ^{68}Ga-DOTATATE



VUMC represents an ongoing academic study, with preliminary unpublished results included in the above plots for comparison

3.4 Evaluation of Safety

There are no safety concerns. There were no reported deaths, SAEs, or significant AEs. Please refer to the clinical report for details.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Due to the nature of data collection based on published papers and 505(b)(2) submission, the information on race, and age was limited.

4.2 Other Special/Subgroup Populations

The summary data submitted from the literature review did not provide information about special/subgroup populations. Also the low number of publications included and the relative homogeneity of the populations, designs and methodology between the studies, no subgroup analysis were performed regarding ^{68}Ga-DOTATATE imaging performance.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This was a 505(b)(2) NDA submission based on a survey of abstracts of recent scientific and medical literature conducted to identify areas of current interest in ^{68}Ga-DOTATATE from a clinical perspective. The sponsor is seeking an indication for (b) (4) The data submitted was a literature review. A systematic review was conducted on PubMed, a service of the US National Library of Medicine. This included the Medline and Toxline core databases. This resulted in 13 studies that met all the inclusion criteria and were used for the final analysis.

The primary analysis planned per meta-analysis protocol was a direct comparison of ^{68}Ga-DOTATATE and Octreoscan based on testing for non-inferiority of the two HSROC areas by a one sided chi-square test. However, the number of publications fulfilling the inclusion/exclusion criteria of the literature review was limited. Due to the lack of adequate published data, a direct comparison of ^{68}Ga- DOTATATE and ^{111}In-pentetreotide (primary analysis) planned in the meta-analysis protocol and Statistical Analysis Plan (SAP)) was not possible. Therefore, sponsor stated that the selection of a non-inferiority margin was not necessary. (Note: this was not communicated to the agency any time prior to information request by the Agency). The sponsor submitted SAP, Agency reviewed it but before the Agency could send the comments to the sponsor, the NDA was submitted.

Therefore, the sponsor focused on the specified secondary endpoints of performance evaluation (such as sensitivity and specificity) per protocol. This included estimates of performance parameters including meta-analysis results of ^{68}Ga-DOTATATE pooled sensitivity and pooled specificity of available qualifying published papers. The standard of truth used in the classification of true positive/negative and false positive/negative, for all included studies, was based upon a composite of conventional imaging (CT/MRI), clinical information, and/or histopathology.

The articles attempted to address changes in management but the information in the articles was lacking sufficient detail. Due to the lack of publication reporting relevant data for ^{68}Ga-DOTATATE compared to ^{111}In-pentetreotide, and the heterogeneity in the methodology used to assess the change in patient management, formal meta-analysis per protocol was not conducted on change in patient management.

There were three comparative studies. There was one published article - prospective, non-randomized, single center, open-label, comparative study conducted at the Vanderbilt University Medical Center (VUMC). There were 2 other articles that were retrospective and blinded that

compared to OctreoScan with conventional imaging (CI) as the Standard of Truth (SOT). Other articles were retrospective and unblinded. The patient populations were metastatic, suspected recurrence, post-operative and few primary presentations.

For the prospective VUMC study, a total number of 97 adult patients with known or suspected neuroendocrine tumors (mean age 54±11; 58% female; 68% of primary tumor localized in the gastroenteropancreatic area, 12% of unknown primary localization, and remaining 20% were hindgut or rectum or pulmonary or symptoms only were enrolled. ^{111}In-pentetreotide scan type for all 97 patients included planar (5%), SPECT (31%), SPECT/CT (52%) and missing (12%). All 97 patients received one injection of ^{68}Ga-DOTATATE on the day of the medical imaging. Average Activity administered was 5.3 mCi (SD 0.3, range 4.3 to 6.0 mCi) and average time between administration and image acquisition was 65 minutes (range 55 to 93 minutes). Median (Quartiles) number of days between ^{111}In-pentetreotide and ^{68}Ga-DOTATATE scans was 176 (105; 354).

There were 78 evaluable patients with comparable scans in this study. The standard of truth was a composite of previous conventional imaging (CT and/or MRI) and histopathology assessment of resected specimen. All investigational scans were read by at least two experienced board-certified nuclear medicine physicians (blinded to the patient's identity and to any other clinical information prior to initial interpretation.) Discrepancies were resolved by consensus of the two interpreting physicians or, in event of failure to reconcile, by a third physician.

When directly comparing the imaging performance of these two products, the sensitivity for ^{68}Ga-DOTATATE was statistically significantly superior to ^{111}In-pentetreotide (96% [95% CI: 86, 100] vs. 72% [58, 84]; McNemar's chi^2, p = 0.003). This difference was mainly explained by the lower number of false negative for ^{68}Ga-DOTATATE (2 cases) compared to ^{111}In-pentetreotide (14 cases). However, the difference observed in the specificity was not statistically significant (93% [77, 99] for ^{68}Ga-DOTATATE vs. 89% [72, 98] for ^{111}In-pentetreotide; McNemar's chi^2, p = 1.000).

A total of 13 studies met all the inclusion criteria for inclusion for the Meta-analysis. Out of these 13 studies 9 qualified for pooled sensitivity estimation based on meta-analysis and 5 qualified for pooled specificity. The pooled sensitivity based on meta-analysis for ^{68}GaDOTATE was 90% with 95% CI (86 – 100%) and for 5 qualified studies, the pooled specificity was 90% with 95% CI (84% - 95%). The details are given in the following Table 11.

Table 11: Sensitivity & Specificity patient-based estimates for ^{68}Ga-DOTATATE All Studies

Author/Year[1]	Design [2]	# Patients	# TP+FN	# TP (detected)	Patient-Based Sensitivity (%) 95% CI	# TN+FP	# TN (detected)	Patient-Based Specificity (%) 95% CI
Comparative Studies								
VUMC 1990	P	78	50	48	96 (86-100)	26	3	93 (76 – 99)
Srirajaskanthan 2010	R	51	47	41	87 (74-95)	4	4	100 (40 – 100)
Hofman 2012	R	59	52	0	100 (93 – 100)	7	6	86 (42 – 100)
Non-comparative Studies								
Alonso 2014	R	29	29	23	79 (6- - 92)	NA	NA	NA
Haug 2014	R	45	18	17	94 (73 – 100)	27	24	89 (71 – 98)
Haug 2012	R	104	36	29	81 (64 – 92)	68	61	90 (80 – 96)
Haug 2009	R	25	25	24	96 (80 -100)	NA	NA	NA
Kayani 2008	R	38	38	31	82 (66-92)	NA	NA	NA
Wild 2013	R	18	18	17	94 (73 - 100)	NA	NA	NA
Meta-Analysis All Studies					90 (86 - 93)			90 (76 – 99)

[1]First author & Year of Publication

[2]Design: P = Prospective R = Retrospective NA = Not Available

Note: VUMC represents an ongoing academic study, with preliminary unpublished results included in the above.

5.2 Conclusions and Recommendations

The application contains a prospective comparative study (VUMC) that shows that the sensitivity of ^{68}Ga-DOTATATE (96% [95% CI: 86, 100] was significantly superior to the sensitivity of comparator product ^{111}In-pentetreotide [72% CI: 58, 84]. The specificity of two product was similar 93% [95% CI 77, 99] for ^{68}Ga-DOTATATE vs. 89% [95% CI 72, 98] for ^{111}In-pentetreotide. %). A systematic review of literature and meta-analysis showed that the pooled sensitivity based on meta-analysis for ^{68}GaDOTATE was 90% with 95% CI (86 – 100%) and the pooled specificity was 90% with 95% CI (84% - 95%). These results show support for approval of the product for an indication for imaging in the detection of somatostatin receptor bearing [(b) (4)] NETS.

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APPENDIX – Meta-Analysis Methodology per Statistical Analysis Plan (Sponsor)

Objectives

The objectives of the meta-analysis were to perform a systematic review and, if sufficient data were available, to conduct a meta-analysis to assess the imaging performance, impact on disease management, and safety of ^{68}Ga-DOTATATE PET/CT in patient with pulmonary or GEP NETs overexpressing somatostatin receptors, compared to ^{111}In-DTPA-Octreotide imaging. If ^{68}Ga-DOTATATE was seen to be equivalent (non-inferior) to or better than ^{111}In-DTPA-Octreotide imaging in safety and diagnostic efficacy, these results would help lead to routine use of ^{68}Ga-DOTATATE as the SRS agent of choice for patients with tumors with high somatostatin receptor expression levels.

Endpoints

The primary endpoint was the difference in imaging performance between ^{68}Ga-DOTATATE PET/CT to ^{111}In-DTPA-Octreotide SPECT imaging performance, as assessed by summary receiver operator characteristic (SROC) curves. The hypothesis was that ^{68}Ga-DOTATATE was considered effective if its imaging performance was non-inferior to that of the current image standard ^{111}In-DTPA-Octreotide.

In addition to the primary endpoint, the secondary endpoint was to demonstrate the non-inferiority of ^{68}Ga-DOTATATE PET/CT compared to ^{111}In-DTPA-Octreotide SPECT for changes in patient management. A further exploratory analysis of ^{68}Ga-DOTATATE PET/CT imaging performance and clinical impact on disease management could have been conducted in a sub-group analysis based upon study characteristics likely to generate heterogeneity. However, due to the limited number of papers identified by the systematic review, the formal non-inferiority and sub-group analyses could not be conducted.

Safety was measured by counts of individuals reporting adverse events (AEs) following use of ^{68}Ga-DOTATATE, with such events being reviewed and summarized in tabular form by toxicity grade, if applicable. However, the majority of the papers identified by the systematic review did not specify any AEs so this tabulation was not conducted.

METHODS

Database Searches

The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for the publication of systematic reviews and meta-analyses. Study selection and the systematic review definition of objectives with clinical relevance followed the Population, Intervention, Comparison, Outcome, and Study Type (PICOS) method.

Medline, EMBASE, and Cochrane Reviews electronics databases were searched from 01 January 1999 through 27 May 2015 without language restrictions (literature was included if the article was in English or English abstract translation was available for non-English articles). Article search criteria include all expression of pulmonary or GEP NETs, including "pulmonary", "lung", "bronchial", "bronchus", "carcinoid, "neuroendocrine", any" gastroenteropancreat*", "stomach", pancreas", "kidney", "gut", etc. Separately any of the

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common expressions of DOTATATE, octreotide, pentreotide, somatostatin or somato-derived receptors were included in the literature search. In addition, bibliographies from meta-analyses and literature reviews were examined individually and papers of interest included in the final list of abstracts for review.

Data Extraction

Abstracts were collected by a research librarian and reviewed independently by two clinician reviewers who were blinded to the other reviewers' results. After abstract review, if either reviewer considered that full data extraction should be conducted, then a complete text review of the article was conducted and data extraction conducted independently by two clinician reviewers with a systematized data extraction tool. After complete article review and data extraction, the two reviewers determined which studies to include in the final systematic review by consensus with a third independent clinician reviewer.

Inclusion-Exclusion Criteria

In order to be included in this analysis, a study had to comply with the following inclusion criteria:

1) Study design and quality:
   a) All study designs such as randomized, not randomized, blinded, open-label, prospective and retrospective, etc.
   b) Published from 01 January 1999 until 27 May 2015
   c) Compared ^{68}Ga-DOTATATE PET/CT imaging to ^{111}In-DTPA-Octreotide SPECT imaging performance
   d) Reported enough data to draft an imaging performance 2x2 contingency table
   e) Used histology, conventional imaging, clinical information or a combination of these as the standard of truth for tumor assessment.
2) Patient population:
   a) Primary data in humans
   b) All ages
   c) All genders
   d) Suffering from pulmonary or GEP NETs, complying with the following criteria:
      i) Embryonic site of origin; (1) Foregut:
         (a) Broncho-pulmonary, also known as "pulmonary" NETs
         (b) Stomach
         (c) Pancreas
         (d) Duodenum to the ligament of Treitz
      (2) Midgut (entire small intestinal tract distal to the ligament of Treitz, including the appendix and right hemi-colon to the distal transverse colon). Note: NETs from the foregut (except pulmonary) and midgut, plus the pancreas, are frequently referred to as GEP NETs.
      (3) Hindgut (including rectum).
      (4) Publications reporting patients with metastatic disease from an unknown primary NET or in patients where studied imaging modalities were used to search for an unknown primary NET. In these cases it was assumed that the primary tumor was

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from the pulmonary or GEP groups since these two groups comprise about 90% of NETs.

Any study that complied with at least one of the following exclusion criteria were not included in the analysis:

1) Publications which were either systematic reviews or case reviews
2) The study population was limited to 10 or less patients
3) The study population included other cancers without any possibility of extracting the data only concerning pulmonary and GEP NETs
4) Publications about tumors from other sites of origin than GEP or pulmonary NETs (e.g. ovary or nasopharynx NETs), because they are extremely rare, and are often reported either as a single case or a short case series, precluding meaningful statistical analysis.
5) The study included other imaging agents without any possibility for extracting the data only concerning ^{68}Ga-DOTATATE and ^{111}In-DTPA-Octreotide
6) The ^{68}Ga-DOTATATE imaging modality was not PET
7) Publications with study populations included in multiple publications. Publications were excluded so that the population under study contributed only once to the meta-analysis. Authors were contacted if necessary to determine the uniqueness of a study population or when data were incomplete. Duplicate populations, in whole or in part, were excluded. When individual patients could not be determined, then the most recent publication was chosen for inclusion.

Quality Measurement

Two reviewers independently assessed the quality of each study according to prospective criteria using a modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS) set of 13 questions. These questions addressed the technical quality of the index test, the technical quality of the reference test, the independence and accuracy of the test interpretation, and the sample size and population representation. Additional quality questions specifically measured possible mis-classification bias arising from incomplete diagnosis, or verification bias arising from only pathological determination of diagnosis driven by scan results. Cochrane collaborative grades were to be investigated if the literature search resulted in findings of randomized controlled trials, randomized interventions or observational cohorts; however, no such studies were identified. Study quality was graphically reviewed and if applicable, sub-analysis conducted on prospective versus retrospective studies, pathological diagnosis versus both pathological and radiographic determination of diagnosis, and studies that blinded reviewers to patient demographic and history versus those that did not (Note: these sub-analyses were not conducted due to the small number of eligible studies identified from the systematic review).

Study Synthesis and Meta-Analysis

Summary sensitivity, specificity, and accuracy with 95% confidence intervals (CIs) were calculated for each imaging method/product by study when possible, though some studies only reported subjects with a known diagnosis of pulmonary or GEP NET, precluding specificity measurements. Summary statistics were to be conducted separately for diagnosis and staging, but this was not possible from the data obtained from the systematic review. Overall test

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performance was estimated in a pooled fashion using forest plots and a SROC. Study heterogeneity was quantitatively measured by Cochran Q and I^2 statistics.

Considerable heterogeneity is expected in diagnostic studies and if possible, a meta-analysis model summarizing test performance was to be estimated. A random effects regression model was calculated to summarize test performance and estimate overall test accuracy. These models were formulated so that the test results were conditioned on the probability of disease. This approach allowed both fixed and random effects modeling of clinically relevant variables. For variables with missing data, multiple imputation with chained equations was planned to be performed using predictive mean matching to estimate missing data. Accepted statistical practices for multiple imputations were to be used. However, due to the small number of studies identified, this missing data imputation was not conducted.

Safety data for the use of ^{68}Ga-DOTATATE was also reviewed and summarized. This included any reported toxicity in the original publication, plus any additional information requested from the correspondence authors if limited or no toxicity reporting occurred in the reviewed study.

Statistical Analysis

All studies included in the meta-analysis were to be analyzed. The main analyses of the primary efficacy endpoint, secondary efficacy endpoint, and safety endpoint were to be performed on the Full Analysis Set. No adjustment was applied for multiple testing.

A descriptive summary of the design and quality of the studies included in the meta-analysis was provided based upon the following variables, where available:

- Study duration (calculated as the difference between study end and begin dates)
- Study type, recorded as one of the following 5 categories: prospective cohort, retrospective cohort, single arm trial, multi-arm randomized clinical trial, not reported
- Type of scanner equipment
- Radiotracer posology/dosing
- Nature/type of standard of truth for determining diagnosis
- Radiologist blinding at the time of reading
- Number of reviewers
- Format of data reviewed
- Basis for determining avidity
- Number of levels of risk reported
- Study purpose recorded as the following 4 categories: diagnostic study only, staging only, safety only, and combination of all.
- Total number of patients
- Number of lesions reviewed
- Impact of test result on final treatment

In addition, study quality was assessed, summarized and presented according to the modified QUADAS set of 13 questions.

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All efficacy variables were listed by study. Data were summarized by imaging agent, with N, missing data, mean, median, standard deviation (SD), first and third quartiles, minimum and maximum summarized for continuous efficacy variables, and count and percentage used to summarize categorical efficacy variables. Agreement between reviewers for study eligibility was calculated by observed percent agreement and the kappa coefficient for inter-rater reliability, with agreement over 80% considered high agreement. Overall test performance was estimated in a pooled fashion using forest plots and SROCs.

To test the pooling assumptions, study heterogeneity was quantitatively measured by Cochran Q and I^2 statistics and assessed graphically by forest plots and an unadjusted SROC. A chi-square test was applied to determine if random effects were present. If not stated otherwise, all tests were two-tailed at the 5% significance level.

Sensitivity was defined as the percentage of patients found to be positive with the imaging procedure among the number of patients positive with the standard of truth:
Sensitivity %= (true positive [TP]/disease positive [DP])*100

Specificity was defined as the percentage of patients found to be negative with the imaging procedure among the number of patients negative with the standard of truth:
Specificity % = (true negative [TN]/disease negative [DN])*100

The non-inferiority of ^{68}Ga-DOTATATE imaging performance compared to ^{111}In-DTPA-Octreotide imaging performance was to be tested as follow:

- The degree of study-to-study heterogeneity was measured by Cochran Q and I^2 statistics and were visually assessed in forest plots.
- Study specific test performance with 95% CIs were displayed in forest plots.
- A 95% CI for the unadjusted overall sensitivity and specificity was reported.

However, this non-inferiority analysis was not conducted due to the small number of eligible studies identified from the systematic review. Therefore only ^{68}Ga-DOTATATE imaging performance pooled estimates were calculated using an unadjusted random effect model (DerSimonian Laird method), which incorporates variation among studies. The CIs of overall sensitivity and specificity were calculated using the F distribution method to compute the exact CIs for the binomial proportion. In addition, the diagnostic odds ratios were combined by the DerSimonian Laird method to estimate the overall diagnostic odd ratio and hence to determine the best-fitting SROC curve and its 95% CI.

A meta-analysis model was to be estimated if more than 10 studies were found through the systematic review. Only 2 direct comparative studies to ^{111}In-DTPA-Octreotide were identified from the systematic review so this formal meta-analysis was not done. Impact on patient management was also to be assessed in both imaging agent groups based upon counts of scan results that caused the clinical care givers to change treatment between the two methods compared to a gold standard of diagnosis, e.g. change within modality such as changes to planned surgery etc.) or across modalities (e.g. add chemotherapy or radiation therapy to surgery etc.).

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In addition to the systematic review, unpublished data from a clinical study conducted in 2015 by Vanderbilt University Medical Center (VUMC), Nashville, TN, USA was provided and included in the overall assessment of ^{68}Ga-DOTATATE, thus allowing more robust descriptive conclusions to be drawn on the efficacy of ^{68}Ga-DOTATATE.

Safety data were to be summarized by anatomical group and toxicity grade for each imaging agent, however, none of the papers identified by the systematic review provided sufficient safety data for this review to be conducted.

Systematic Review

There is limited comparison to the current established standard of ^{111}In-DTPA-Octreotide imaging for the same indications. Instead, reviews often combine several different ^{68}Ga-labeled synthetic somatostatin analogs, with inconsistent imaging protocols, radiopharmaceutical synthesis methods, and tumor types. Via correspondence with authors, we also determined that some prior reviews did not separate studies with overlapping patient populations. The lack of direct, controlled comparison of ^{68}Ga-DOTATATE PET/CT imaging with ^{111}In-DTPA-Octreotide imaging hinders direct assessment of differential efficacy between these two radiopharmaceuticals.

The electronic search returned 2,378 articles, with one additional article added from bibliography reviews, giving a total of 2,379 study abstracts screened. After the initial abstract review, 2,344 articles were excluded. Agreement between reviewers for study inclusion was 99%. An article could be excluded for multiple reasons, but the most common reasons for exclusion during the initial review were that the article described treatment and not diagnosis with ^{68}Ga-DOTATATE (N=578), the radiopharmaceutical was not ^{68}Ga-DOTATATE (N=729), or the article was a case review with the number of participants less than 10 (N=674).

Thirty-five studies received a full review, of which 22 were excluded upon closer analysis. The remaining 13 studies met all the inclusion criteria and were used for the final analysis (Figure 1). The 13 studies included a total of 579 subjects, with an average age of 55 years (95% CI: 50, 60). Across the 13 studies, two studies reported a direct comparison of ^{68}Ga-DOTATATE to ^{111}In-DTPA-Octreotide and conventional imaging (Srirajaskanthan 2010; Hofman 2012), eight studies compared ^{68}Ga-DOTATATE to conventional imaging of CT or MRI only (Kayani 2008; Haug 2009; Haug 2012; Poeppel 2013; Wild 2013; Alonso 2014; Etchebehere 2014; Haug 2014) and three studies reported comparison of ^{68}Ga-DOTATATE to other investigational radiopharmaceuticals with no other direct imaging comparator, although each did have information regarding the safety, toxicity and method of radiopharmaceutical administration (Lapinska 2011; Brogsitter 2014; Ilhan 2014).

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/s/

SATISH C MISRA
12/14/2015

JYOTI ZALKIKAR
12/14/2015
I, as a secondary reviewer, generally concur with the primary reviewer.

THOMAS E GWISE
12/15/2015

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	208-547
Drug Name:	(b) (4) (^{68}Ga-Dotatate Injection)
Proposed Indication:	(b) (4) neuroendocrine tumors (b) (4) NETs)
Applicant:	Advanced Accelerator Applications (AAA)
Date(s):	NDA submission: July 1, 2015
	PDUFA Date: March 1, 2016
Review Priority:	Priority (Orphan drug product)
Biometrics Division:	OB V
Secondary Statistical Reviewer:	Jyoti Zalkikar, Ph.D.
Concurring Reviewers:	Thomas Gwise, Ph.D.
	Deputy Director, Division of Biometrics V
Medical Division:	Division of Medical Imaging
Clinical Team:	Reviewer: Cynthia Welsh, M.D.
	TL: Nushin Todd, M.D.
Project Manager:	Modupe Fagbami
Keywords:	Sensitivity, Specificity, Confidence intervals, Meta-Analysis

EXECUTIVE SUMMARY

^{68}Ga-DOTATATE is a radiopharmaceutical product used for functional imaging with positron emission tomography (PET) when the increased expression of SSTR, particularly of subtype 2 is a diagnostic target. Several types of tumors are known to significantly express SSTR. According to the applicant, among those tumors of different primary origin and variable clinical behavior, the functional imaging with ^{68}Ga-DOTATATE is currently sufficiently documented in (b) (4) neuroendocrine tumors ((b) (4) NET).

The Applicant was granted access to the results of a prospective comparative study conducted at the Vanderbilt University Medical Center (VUMC): "^{68}Ga-DOTATATE PET Scan in Neuroendocrine Cancer," (VUMC IRB Protocol #110588; NCT01396382). The objective of this study was to compare ^{68}Ga-Dotatate PET scan imaging to the existing (standard-of-care) somatostatin receptor imaging agent, ^{111}In-pentetreotide. This study did not use AAA manufactured ^{68}Ga-DOTATATE kit, but radio-pharmacy at VUMC tested the Advanced Accelerator Applications (AAA) ^{68}Ga-DOTATATE Kit and found that the Kit reproducible, comparable and equivalent in radiochemical purity to the preparation they manufactured "in-house".

The AAA manufactured Kit for the Preparation of ^{68}Ga DOTATATE has not yet been administered to humans. Clinical trials sponsored by the Applicant with their ^{68}Ga-DOTATATE Kit as an investigational medicinal product are not planned.

This application is based on efficacy and safety data of ^{68}Ga-DOTATATE from a prospective comparative clinical study conducted at the VUMC and critical overview of available literature data supported by a meta-analysis of published results of clinical studies with ^{68}Ga-DOTATATE. Based upon the review of the submitted information to date, it is unlikely the Medical Division (DMIP) will be able to grant the indication the applicant is seeking. The VUMC results and the data in the literature are insufficient to describe applicant's indication in the label for the population of patients with (b) (4) NETs. However, after consideration, the totality of the submitted data might be sufficient for the following (working) indication statement: "A kit for the preparation of ^{68}Ga-DOTATATE indicated for positron emission tomography (PET) imaging, as an adjunct to other diagnostic tests, in the localization of neuroendocrine tumors (NETs) in adult and pediatric patients."

The readers should read the following brief review from this (working) indication point of view.

The VUMC study was an investigator sponsored Phase I/II study, designed to explore the safety and efficacy performance of ^{68}Ga-DOTATATE PET vs Octreoscan SPECT. No primary endpoint was selected per protocol a priori. In this published non-randomized, single center, open-label study comparing ^{68}Ga-DOTATATE and ^{111}In-pentreotide in 97 adult patients with known or suspected neuroendocrine tumors (mean age 54±11; 58% female; 68% of primary tumor localized in the gastroenteropancreatic area, 12% of unknown primary localization, and remaining 20% were hindgut or rectum or pulmonary or symptoms only. ^{111}In-pentetreotide scan type for all 97 patients included planar (5%), SPECT (31%), SPECT/CT(52%), and missing (12%). All 97 patients received one injection of ^{68}Ga-DOTATATE on the day of the medical imaging. Median (Quartiles) number of days between ^{111}In-pentetreotide and ^{68}Ga-DOTATATE scans was 176 (105; 354). There were 78 evaluable patients with comparable scans (10 had no Pentetreotide scan, 5 had no post-surgical

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Pentetreotide, and time between scans was > 3 years for 4 patients). The tumor location in these 78 patients were bowel (37), gastric (18), CUP (7), symptoms only (7), pulmonary (5), hindgut (3) and other (1). The standard of truth was a composite of previous conventional imaging (CT, MRI and ^{111}In-Octreotide scans) and histopathology assessment of resected specimen. The information regarding which patients had histopathology and which patients had conventional imaging was not available from the applicant. When directly comparing the imaging performance for 2 blinded readers with consensus read by an un-blinded reader to resolve discrepancies of these two readers for 78 patients, the sensitivity for ^{68}Ga-DOTATATE was statistically significantly superior to ^{111}In-pentetreotide (96% [95% CI: 86, 100] vs. 72% [58, 84]; McNemar's chi^2, p = 0.003). This difference was mainly explained by the lower number of false negative (according majority read) for ^{68}Ga-DOTATATE (2 cases) compared to ^{111}In-pentetreotide (14 cases). However, the difference observed in the specificity was not statistically significant (93% [77, 99] for ^{68}Ga-DOTATATE vs. 89% [72, 98] for ^{111}In-pentetreotide; McNemar's chi^2, p = 1.000).

This secondary reviewer found several limitations with this study including the following: 1> Standard of truth is composite with histopathology and conventional imaging including scanning by CT, MRI and ^{111}In-Octreotide scans. This conventional imaging was determined prior to ^{68}Ga-DOTATATE PET scanning and may have changed the management of some of the patients. 2> Scanning with the comparator of currently approved product, ^{111}In-pentetreotide, was done prior to this study taking place and was not done in this study. This makes approved product (^{111}In-pentetreotide) unsuitable for comparison. Besides that those scans may have an effect on management of some of the patients. 3> Information regarding histopathology was not made available to the review team by the applicant, but this information was perhaps available to un-blinded reader doing the adjudication in case of discrepancies of the 2 blinded readers. This has the potential to inflate the performance characteristics of ^{68}Ga-DOTATATE.

The following table gives the information regarding 2 blinded reads for ^{68}Ga-DOTATATE for all 97 patients giving sensitivity of 97% (95% CI: 93-100) and 95% (95% CI: 89 – 100) respectively and specificity of 81% (95% CI: 67 – 95) and 77% (95% CI: 62 – 92) respectively.

Blinded Read	Reader 1	Reader 2
SOT not available	7	7
Correct	82	80
False Negative	2	3
False Positive	6	7

According to the primary statistical reviewer, in a meta-analysis of 9 literature based qualified studies per inclusion/exclusion criteria, the pooled sensitivity for ^{68}GaDOTATE was 90% with 95% CI (86 – 100%) and for 5 qualified studies, the pooled specificity was 90% with 95% CI (84% - 95%). There is no safety risk from the drug and no adverse events have been reported.

From this totality of the submitted data, ^{68}Ga-DOTATATE is approvable for the (working) indication statement given above, but comparison to another approved drug should be avoided in the section 14 of the label.

Jyoti Zalkikar
Secondary Reviewer, DB V

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JYOTI ZALKIKAR
12/14/2015

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