CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213227Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2) NDA
Application Number	213227
Priority or Standard	Priority
Submit Date	7/8/2019, 1/3/2020
Received Date	7/8/2019, 1/3/2020
PDUFA Goal Date	9/3/2020
Division/Office	Division of Imaging and Radiation Medicine/Office of Specialty Medicine
Review Completion Date	9/2/2020
Established/Proper Name	copper Cu 64 dotatate
Trade Name	Detectnet
Pharmacologic Class	Radioactive diagnostic agent
Code Name	5020100
Applicant	RadioMedix, Inc.
Dosage Form	Injection
Applicant proposed Dosing Regimen	148 (b) (4) % MBq (4 (b) (4) % mCi) administered as an intravenous bolus injection
Applicant Proposed Indication/Population	Positron emission tomography (PET) for (b) (4) localization (b) (4) of somatostatin receptor positive neuroendocrine tumors (NETs) in adults
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	C805 Neuroendocrine carcinoma (disorder)
Regulatory Action	Approval
Indication/Population	Positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult patients
SNOMED CT Indication Disease Term	C805 Neuroendocrine carcinoma (disorder)
Recommended Dosing Regimen	148 MBq (4mCi) administered as an intravenous bolus injection

Table of Contents

Table of Tables

Table of Figures

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
OSM= Office of Specialty Medicine
DEPI= Division of Epidemiology
DIRM = Division of Imaging and Radiation Medicine
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
CFR	Code of Federal Regulations
CI	confidence interval
CSR	clinical study report
CT	computed tomography
DOTA	tetraxetan
DTPA	diethylenetriaminepentaacetic acid
ECG	electrocardiogram
EE	efficacy evaluable
FDA	Food and Drug Administration
FDG	F-18 fludeoxyglucose
HPLC	high performance liquid chromatography
IND	Investigational New Drug
MRI	magnetic resonance imaging
NDA	new drug application
NET	neuroendocrine tumor
NME	new molecular entity
NPA	negative percent agreement
PET	positron emission tomography
PK	pharmacokinetics
PPA	positive percent agreement
PREA	Pediatric Research Equity Act
SD	standard deviation
SOT	standard of truth
SPA	special protocol assessment
SPECT	single-photon emission computed tomography
SSTR	somatostatin receptor
SSTR2	somatostatin receptor, subtype 2
US	ultrasound

1. Executive Summary

1.1. Product Introduction

RadioMedix has developed copper Cu 64 dotatate injection (hereafter referred to as Cu-64 dotatate) as a radioactive diagnostic agent for use with positron emission tomography (PET) of somatostatin receptor (SSTR) positive neuroendocrine tumors (NETs) in adults. New drug application (NDA) 213227 is a 505(b)(2) application for this designated new molecular entity (NME). Primary data supporting efficacy and safety were collected in trials conducted by the Applicant, while published data were relied upon without right of reference for human dosimetry and biodistribution data as well as additional supportive evidence of efficacy and safety.

The Cu-64 dotatate molecule has three regions, namely the somatostatin analog octreotate, the chemical linker tetraxetan (DOTA) and the positron emitter Cu-64. The somatostatin analog octreotate binds to SSTRs and is similar to octreotide, except the C-terminal threoninol is replaced with threonine. DOTA-Tyr3-octreotate is a (b) (4) cyclic 8 amino acid peptide covalently conjugated to DOTA, forming DOTA-octreotate (dotatate). Upon radiolabeling, Cu-64 binds to the DOTA portion of the molecule forming Cu-64 dotatate.

The current NDA is the first to be submitted for an imaging drug labeled with a copper radionuclide. Cu-64 emits positrons with an emission yield that allows for PET imaging. It has a half-life of 12.7 hours, which enables manufacturing of the drug product centrally and distribution to other parts of the U.S. The relatively long half-life of Cu-64 also facilitates delayed imaging after drug administration. The lower mean positron range, or distance a positron travels from emission until annihilation, is shorter for Cu-64 (1 mm) compared to Ga-68 (4 mm). A shorter range theoretically results in increased spatial resolution. (Kjaer and Knigge 2015).

Cu-64 dotatate will be supplied as a single-dose vial containing 4 mCi/vial (1 mCi/mL) at calibration date and time. The drug product is in a sterile solution of 40 mg/mL ascorbic acid and (b) (4) (v/v) ethanol at a solution pH of 5.5 to 7.5. The drug product is presented in a 10 mL (b) (4) glass vial affixed with a gray (b) (4) rubber stopper (b) (4) and aluminum crimp cap. The sealed vial is contained in (b) (4)
The drug product expires 2 hours after the calibration date and time, ensuring that the desired dose is available for patient administration within the expiration dating period.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness has been provided by the Applicant to adequately support approval. Study RMX-18-22 was a prospective trial conducted by the Applicant that met pre-specified success criteria for all three blinded, independent PET readers for positive and

negative percent agreement of Cu-64 dotatate PET with a composite reference standard for NET. These results were collected predominantly in the population of intended use at a single U.S. center and were further supported through the Applicant's re-analysis of published clinical data in the NETMedix Denmark trial. This re-analysis provided similar estimates of Cu-64 dotatate imaging performance in a larger population of adult NET patients studied at a single site in Denmark. While certain weaknesses are present in the two studies, the shortcomings are outweighed by the robust imaging efficacy results, particularly given the orphan drug population for which the product is intended. Additional factors to consider are the physical characteristics of Cu-64 as a radiolabel and the history of extensive clinical experience with multiple somatostatin analogs for both diagnostic and therapeutic purposes in patients with NET.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

A prospective trial conducted by the Applicant along with additional support from the Applicant's re-analysis of published clinical data adequately demonstrate the efficacy of Cu-64 dotatate positron emission tomography (PET) for imaging of somatostatin receptor (SSTR) positive neuroendocrine tumors (NETs) in adults. Available clinical data also adequately support the safety of Cu-64 dotatate. Cu-64 dotatate is expected to expand the current availability of SSTR PET for NET. The benefit-risk balance of Cu-64 dotatate for NET imaging in adults is favorable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• NETs are a heterogeneous and rare group of usually slow-growing malignancies. • NETs can arise almost anywhere in the body and cause significant morbidity and mortality. Approximately 20% of patients present with metastatic disease at the time of diagnosis. • Well-differentiated NETs typically express high levels of SSTRs on their cell surface.	SSTRs provide an important target for diagnostic imaging and treatment of NETs.
Current Treatment Options	• In addition to standard anatomic imaging modalities, radiotracers based upon somatostatin analogs that target SSTRs have been approved to image NET as described below. • In-111 pentetreotide is compatible with planar and single-photon emission tomography (SPECT) • Ga-68 dotatate and Ga-68 dotatoc are compatible with PET and provide imaging characteristics, including imaging efficacy, spatial resolution, and signal quantitation, that favorably affect image quality, duration of imaging procedures, and absorbed radiation doses.	While Ga-68 dotatate and Ga-68 dotatoc PET have provided important new imaging options, they have been associated with limited availability to patients. Cu-64 is PET-compatible, (b) (4) and has a relatively long half-life of 12.7 hours. As such, Cu-64 dotatate has the potential to allow nationwide distribution of an SSTR PET agent from a central manufacturing source without dependence on Ga-68 generators.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Ga-68 dotatoc is currently approved for manufacturing at one U.S. site. Regional distribution from this site would not be practical due to the 68 minute half-life of Ga-68. • Ga-68 dotatate is approved as a cold kit that can be distributed broadly and radiolabeled at any site that has a Ge-68/Ga-68 generator.	
Benefit	• The Applicant conducted a prospective trial in the U.S., Study RMX-18-22, and a supportive re-analysis of published clinical data collected abroad, the NETMedix Denmark Trial. Both studies showed good positive and negative percent agreement of Cu-64 dotatate PET with a composite reference standard for NET in an adult population consisting predominantly of patients with NET history. • Study RMX-18-22 met pre-specified success criteria for imaging performance in all three blinded, independent PET readers. • Weaknesses were present in the reference standards of both studies. • The NETMedix Denmark Trial used consensus instead of independent PET reads. • Healthy volunteers were included in Study RMX-18-22.	Weaknesses in the supporting trials are outweighed by the robust imaging efficacy results, particularly when considering the orphan disease population of intended use. Additional favorable considerations are the physical characteristics of Cu-64 as a radiolabel and the history of extensive clinical experience with multiple somatostatin analogs for both diagnostic and therapeutic purposes in patients with NET.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• No deaths or other serious adverse events were reported in the available safety database of 71 subjects studied in prospective trials conducted by the Applicant and 126 patients from the published literature with safety results. • The safety database revealed only infrequent cases of flushing, nausea, and vomiting as adverse reactions. • An additional published abstract reported no major side-effects in 374 additional NET patients who received Cu-64 dotatate (Kjaer et al. 2019). • Radiation exposure from the proposed 4 mCi administration of Cu-64 dotatate is estimated to impart an effective dose of 4.7 mSv.	Although the available safety database is relatively small, it appears sufficient to support the safety of Cu-64 dotatate given the lack of concerning signals, the proposed microdosing, and the orphan disease population. Estimated effective dose from radiation exposure is within the range of other commonly used diagnostic radiopharmaceuticals, including those used for PET imaging of NET.

1.4. Patient Experience Data

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):		
X	**Patient experience data were not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

NETs are a heterogeneous and rare group of usually slow-growing malignancies. NETs arise from the diffuse neuroendocrine cell system with localization almost anywhere in the human body, but are most commonly found in the pancreas, small intestine, and the lungs. The clinical behavior of NET is variable, with each anatomic site being associated with distinct features such as morphology, expression of markers, and clinical syndromes caused by secretion of hormones and other substances. NETs cause significant morbidity and mortality. Approximately20% of patients present with metastatic disease at the time of diagnosis.

Well-differentiated NETs typically express high levels of SSTRs on their cell surface, the most common being somatostatin receptors, subtype 2 (SSTR2). Cu-64 dotatate binds to SSTRs with highest affinity for SSTR2. Poorly-differentiated neuroendocrine carcinomas may not express high levels of SSTRs.

2.2. Analysis of Current Treatment Options

Diagnostic imaging options for NETs include general anatomic modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) as well as functional imaging modalities including single-photon emission computed tomography (SPECT) and PET.

Functional NET imaging using somatostatin analogs that bind SSTRs was first established with In-111 pentetreotide (OctreoScan, approved in 1994) which is compatible with SPECT and planar imaging. Recent approval of two additional somatostatin analog imaging drugs, Ga-68 dotatate (Netspot, approved in 2016) and Ga-68 dotatoc (approved in 2019), brought new options to NET imaging. The Ga-68 radionuclide based radiopharmaceuticals provide imaging characteristics, including imaging efficacy, spatial resolution, and signal quantitation, that favorably affect image quality, duration of imaging, and radiation absorbed doses.

Ga-68 dotatoc is approved as a final radiolabeled injection and is currently only manufactured at one U.S. site. Because of the 68-minute half-life of Ga-68, regional distribution of Ga-68 dotatoc from a single site would not be practical. Ga-68 dotatate, on the other hand, is approved as a cold kit that can be distributed broadly and radiolabeled at any site that has a Ge-68/Ga-68 generator. However, there have been limitations in the distribution and availability of such generators..

Cu-64 (b) (4) has a relatively long half-life of 12.7 hours. These features offer the potential for nationwide distribution from a central manufacturing source that is not reliant on generators. Additionally, Cu-64 has a favorable spatial resolution due to its short mean positron range. The half-life of Cu-64 also facilitates delayed imaging or repeat imaging without redosing in cases of image acquisition issues such as patient movement during scanning.

F-18 fludeoxyglucose (FDG) PET, while not specific for SSTR-positive tumors, is another functional imaging technique that may be useful in cases of poorly differentiated neuroendocrine carcinomas. However, FDG PET uptake is typically low or absent in more differentiated NET.

Of note, while not used for diagnostic imaging, Lu-177 dotatate (Lutathera) was approved in 2018 for the treatment of SSTR-positive gastroenteropancreatic NETs. This approval supports the clinical utility of molecules targeting the SSTR receptors in patients with NET.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Cu-64 dotatate is an NME that has not been marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

A pre-investigational new drug (IND) meeting was held on October 4, 2016, during which the Applicant presented literature findings from Pfeifer et al., 2012, and Pfeifer et al., 2015 (Pfeifer et al. 2012; Pfeifer et al. 2015). Due to the relatively low number of patients in the published trials and their reliance on a single study site, the U.S. Food and Drug Administration (FDA) recommended that the Applicant conduct a single-arm, non-comparative trial to replicate the published experience, preferably in the U.S. population.

On May 18, 2016, orphan drug designation was granted to Cu-64 dotatate as a diagnostic for the management of NETs. Therefore, Pediatric Research Equity Act (PREA) requirements are not applicable to this NDA.

A special protocol assessment (SPA) was requested by the Applicant for the prospective phase 3 Study RMX-18-22 on April 6, 2018, and an agreement letter was sent by FDA on May 27, 2018.

Under IND 131797, Fast Track designation was granted for this product on December 19, 2018.

A Pre-NDA meeting was held between the FDA and the Applicant on April 25, 2019. Agreement was reached on the format and content of the NDA submission.

The application was granted rolling review status on June 27, 2019. Module 4 (Nonclinical Study Reports), Module 5 (Clinical Study Reports) and Module 2 summaries (except Quality Overall Summary) were included in the initial submission on July 8,2019. The remainder of the NDA was submitted on January 3, 2020 with product quality data.

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

4.1. Office of Scientific Investigations

The Applicant conducted a phase 3 study (RMX -18-22) as well as a literature-based retrospective analysis (NETMedix Denmark Trial). Since Study RMX-18-22 provided major efficacy results pertinent to decision making, the review team requested to have its single clinical site inspected and its primary efficacy results verified. The Office of Scientific Investigations concluded that no inspection deficiencies were identified, the data used to generate the primary efficacy results were verifiable, and adverse events (AEs) were not underreported.

The review team did not deem it necessary to audit the supporting NETMedix Denmark Trial.

4.2. Product Quality

The product quality aspects (identity, strength, purity and quality) support approval of the NDA. The manufacturing facilities are in acceptable current good manufacturing practice compliance to manufacture the proposed drug product. Office of Pharmaceutical Quality recommends approval of NDA 213227 based on the Integrated Quality Assessment finalized on August 24, 2020.

Clinical Microbiology

This section is not applicable to this NDA.

4.3. Devices and Companion Diagnostic Issues

This section is not applicable to this NDA.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Cu-64 dotatate is a microdose product with a clinical mass dose of less than 100 µg. This dose is sub-pharmacologic, and therefore certain nonclinical data for such an application are not needed, as described in the Guidance "Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations" (https:www.fda.gov/media/107641/download).

Nonclinical studies to evaluate absorption, distribution, metabolism, excretion (ADME)/pharmacokinetics (PK), genetic toxicology, carcinogenicity, and reproductive and developmental toxicology are not typically required for microdose radiopharmaceutical applications and none were submitted to the NDA. A single-dose general toxicology study in a rodent species is typically recommended before initiation of clinical studies for a microdose pharmaceutical to be administered once or infrequently. However, such a toxicology study might not be necessary if adequate clinical data are available. A general toxicology study of dotatate was not conducted. From the review team perspective, there is enough clinical data in the studies conducted by the Applicant and the cited scientific literature to support the conclusion that a general toxicology study is not needed for this application.

The nonclinical review discipline recommends approval of the application.

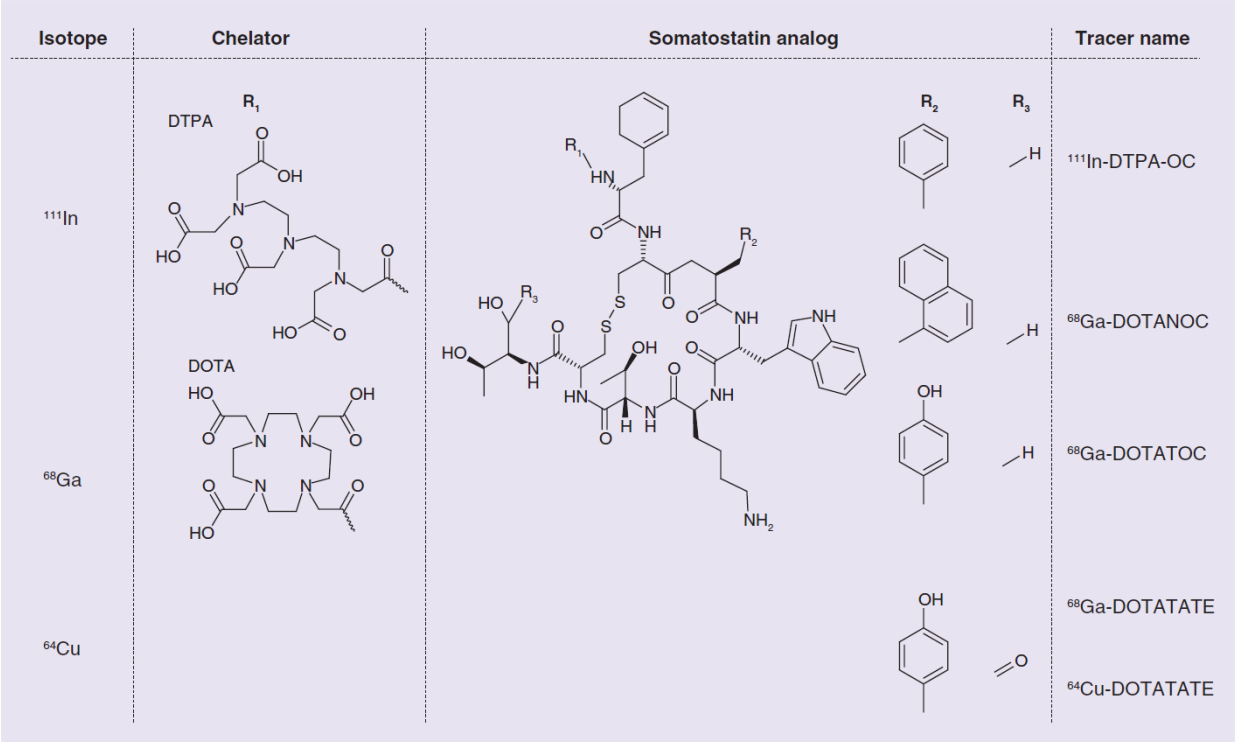
5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

SSTRs are frequently overexpressed in NETs. There are 5 subtypes of SSTRs and the SSTR2 subtype is the most frequently overexpressed subtype in NETs. As illustrated in Figure 1, somatostatin analogs covalently bound to a DOTA or DTPA chelator are suitable pharmacophores for radiolabeling with In-111, Ga-68, or Cu-64 and have been evaluated in clinical studies of patients with NETs (Johnbeck et al. 2014).

Figure 1. Chemical Structure of Somatostatin Analogs, Chelators, and Radioisotopes Evaluated for PET Imaging of NETs



Source: (Johnbeck et al. 2014)

Results from an *in vitro* affinity binding study, suggest that dotatate may be the somatostatin analog with the highest binding affinity towards SSTR2 (Table 1). The applicability of the relative differences shown *in vitro* to the *in vivo* biodistribution is unclear. The study was performed using Ga-68; however, the use of a Cu radioisotope would not be expected to alter dotatate binding to the SSTR compared to the use of a Ga radioisotope.

Table 1. In Vitro Binding Affinities (IC50 in nM ± SEM)

Somatostatin analog	Name	sst1	sst2	sst3	sst4	sst5
Ga-DOTA-Tyr^3-octreotate	Ga-DOTATATE	>10,000	0.2 ± 0.04	>1000	300 ± 140	377 ± 18
Ga-DOTA-Tyr^3-octreotide	Ga-DOTATOC	>10,000	2.5 ± 0.5	613 ± 140	>1000	73 ± 21
Ga-DOTA-octreotide	Ga-DOTAOC	>10,000	7.3 ± 1.9	120 ± 45	>1000	60 ± 14
Ga-DOTA-l-Nal^3-octreotide	Ga-DOTANOC	>10,000	1.9 ± 0.4	40 ± 5.8	260 ± 74	7.2 ± 1.6
DOTA-lanreotide	DOTALAN	>10,000	26 ± 3.4	771 ± 229	>10,000	73 ± 12
In-DTPA-octreotide	In-DTPA-OC	>10,000	22 ± 3.6	182 ± 13	>1000	237 ± 52

DOTA: 1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraacetic acid; DOTALAN: DOTA-lanreotide; DOTANOC: DOTA-l-Nal3-octreotide; DOTATATE: DOTA-Tyr3-octreotate; DOTATOC: DOTA-Tyr3-octreotide; DTPA: Diethylene triamine pentaacetic acid.
Data taken from [35] and, for Ga-DOTANOC, from [44].

Source: (Johnbeck et al. 2014)

Administration of Cu-64 dotatate to A427-7 tumor-bearing Balb/c mice showed an average tumor-to-background uptake ratio of 30.5 and 16.0 at 2 and 24 hours after intravenous injection, respectively (Paterson et al. 2014).

5.4. Toxicology

5.4.1. General Toxicology

General toxicology study reports were not submitted and are not needed

5.4.2. Genetic Toxicology

Genetic toxicology study reports were not submitted and are not needed.

5.4.3. Carcinogenicity

Carcinogenicity study reports were not submitted and are not needed.

5.4.4. Reproductive and Developmental Toxicology

Reproductive and developmental toxicology study reports were not submitted and are not needed.

5.4.5. Other Toxicology Studies

None submitted and none needed

6. Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology has reviewed the information submitted in NDA 213227. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Table 2. Recommendations and Comments for Review Issues of NDA 213227

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness is provided by Study RMX-18-22.
General dosing instructions	The proposed Cu-64 dotatate dose is 4 mCi (148 MBq), administered as a single intravenous bolus injection. In Study RMX-17-22, total image score was comparable between a dose of 4 and 5 mCi. In Study RMX-18-22, all three independent readers demonstrated success on the co-primary imaging efficacy endpoints. The PET/CT image scan was performed in the range of 39 to 97 min after administration of Cu-64 dotatate. Adverse events were observed in 8% of subjects in Study RMX-18-22, none of them serious.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The effect of hepatic impairment or renal impairment on Cu-64 dotatate pharmacokinetics has not been studied.
Drug-drug interactions	No dedicated drug interaction study was conducted. However, non-radioactive somatostatin analogs and Cu-64 dotatate competitively bind to SSTRs.
Labeling	(b) (4) (See Section 15.3).
Bridge between the to-be-marketed and clinical trial formulations	Not applicable.

Abbreviations: CT, computed tomography; PET, positron emission tomography; PK, pharmacokinetic; SSTR, somatostatin receptors

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Distribution

After 1 to 3 hours of a single dose administration of Cu-64 dotatate, the maximum radioactivity is observed in the adrenal glands, kidney, pituitary glands, spleen, and liver.

Elimination

Metabolism

The metabolism of Cu 64 dotatate is unknown.

Excretion

Following a single intravenous dose (4.15±0.13 mCi) of Cu-64 dotatate (n=6), between 16% to 40% of the radioactivity of the injected dose was recovered in urine over a 6-hour collection time.

Specific Populations

The effect of hepatic impairment or renal impairment on Cu-64 dotatate PK has not been studied.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended amount of radioactivity to be administered for PET imaging is 4mCi (148 MBq) administered as an intravenous bolus injection over a period of approximately one minute.

Therapeutic Individualization

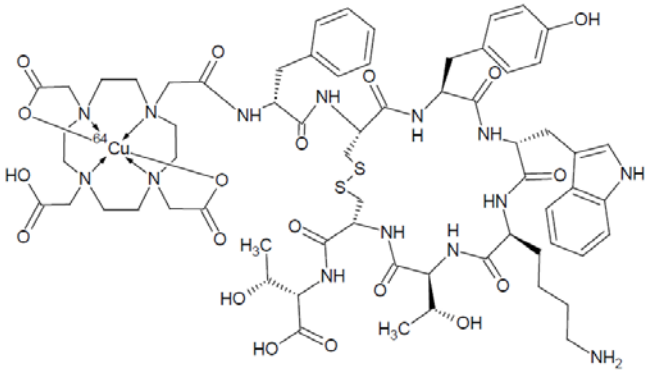
No outstanding issues are identified from a Clinical Pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The general overview of Cu-64 dotatate ADME and clinical PK information are presented below.

Table 3. ADME and Clinical PK Information for Cu-64 Dotatate

Parameter	Information
Physiochemical Properties	
Chemical structure and molecular weight	 **Molecular weight** 1497.5 g/mol **Molecular Formula** $C_{65}H_{88}N_{14}CuO_{19}S_2$ Source: NDA213227, Figure 3.2.S.1-2
Pharmacology	
Mechanism of action	Saturation and Scatchard's analysis of specific Cu-64 dotatate binding to mouse SSTR2 on PMC-mCherry tumor sections showed a B_{max} of 71 fmol/mm^3 tissue and a K_D of 6.2 nmol/L (Ullrich et al. 2016).
Active Moieties	Dotatate binds to SSTR2. Cu-64 releases gamma (γ) radiation and has a physical half-life of 12.7 hours.
Imaging time window post-dose	In Study RMX-18-22, the PET/CT imagining time scan ranged between 39 and 97 min post-dose. The imagining time accepted for labeling is 45 to 90 min.
QT/QTc prolongation	Not applicable
General Information	
Bioanalysis	Cu-64 dotatate in plasma was measured using a HPLC method. However, the method had issues and was considered not validated (See Section 15.3.1 for details).
Healthy volunteers vs. patients	Not applicable
Drug exposure at steady state following the therapeutic dosing regimen	Not applicable
Minimal effective dose or exposure	Not applicable
Maximal tolerated dose or exposure	In Study RMX-17-22, patients were dosed up to 5 mCi. In another study (Pfeifer et al. 2012), patients were dosed up to 6 mCi. The MTD was not reached..
Dose proportionality	Not studied
Accumulation	Not applicable
Variability	Unknown due to bioanalytical issues

Parameter	Information
Distribution	
Volume of distribution	The volume of distribution was not determined due to a lack of PK data. After 1 to 3 hours of a single dose administration of Cu-64 dotatate (Pfeifer et al. 2012), the maximum radioactivity is observed in the adrenal glands, kidney, pituitary glands, spleen, and liver.
Plasma protein binding	Not studied
Blood to plasma ratio	Not studied
Elimination	
Half-life	In Study RMX-18-22, the plasma PK collection time was up to 2 hours. Bioanalytical issues were observed with measuring concentrations of Cu-64 dotatate in plasma PK samples. Thus, the half-life cannot be determined.
Clearance	The total body clearance was not determined due to a lack of PK data.
Metabolism	
Primary metabolic pathway(s)	Not studied
Inhibitor/inducer	Not studied
Excretion	
Primary excretion pathways (% dose) ±SD	For 6 subjects in Study RMX-18-22, radioactivity recovery in urine ranged between 16% to 40% over a 6-hour collection time.

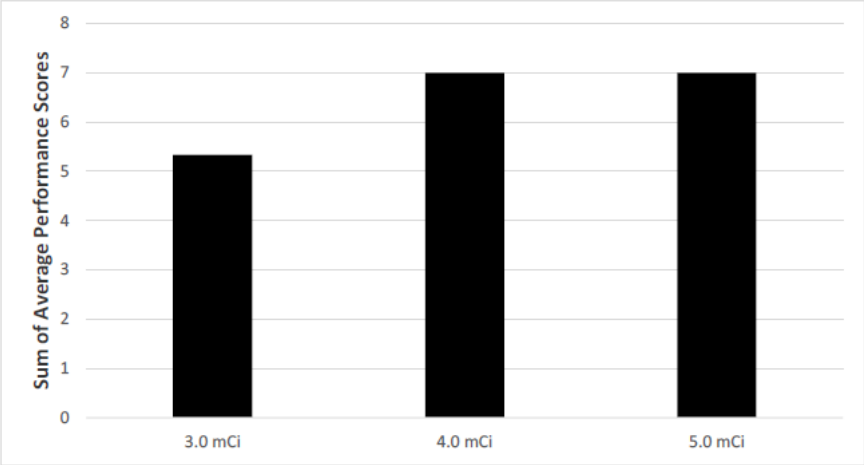
Abbreviations: CT, computed tomography; HPLC, high performance liquid chromatography; PET, positron emission tomography; PK, pharmacokinetic; SSTR2, somatostatin receptor subtype 2

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. In Study RMX-17-22, 12 patients with confirmed NET were divided into 3 dosing cohorts (4 patients each). The patients in each of the dosing cohorts received a mean ± standard deviation (SD) single intravenous bolus dose of 3.09 (±0.04), 4.20 (±0.27), or 5.30 (±0.09) mCi Cu-64 dotatate (Figure 2). A PET/CT scan was performed 60 ± 15 min after dosing. The primary endpoint was total image quality scores by 4 readers. The score was measured on a scale of 0-2 with 0=Inadequate: images look grainy with poor delineation of lesions, 1= Questionable: images are clear but lesion delineation is suboptimal and small lesions (1 cm) are hard to assess, and 2=Acceptable: images are clear and large and small lesion delineation is possible. Based on preliminary analyses, the 3, 4, 5 mCi dose groups showed an average total image score of 5.3, 7, and 7, respectively. Three of 12 patients (25%) experienced mild AEs. No dose-response relationship for safety was observed. A dose of 4 mCi was selected as the recommended phase 2 dose (RP2D).

Figure 2. Sum of Average Patient Imaging Quality Scores by Dose Group in Study RMX-17-22



Source: 5.3.4.2 RMX-17-22 Study report, Figure 11.4, Page 35

The primary evidence of effectiveness was obtained from Study RMX-18-22. A total of 63 healthy volunteers and patients with history of NET or suspicion of NET were evaluated. The subjects were administered a single mean (SD) intravenous bolus dose of 4.11 (±0.17) mCi Cu-64 dotatate. A PET/CT scan was performed in the range of 39 to 97 minutes after administration. The proposed co-primary endpoints were subject-level sensitivity and specificity of Cu-64 dotatate as assessed against a standard of truth (SOT). All 3 blinded PET readers met pre-specified success criteria. The efficacy results from Study RMX-18-22 provide adequate evidence for the effectiveness of Cu-64 dotatate at a 4 mCi dose for PET imaging of somatostatin receptor-positive NETs in adults.

In Study RMX-18-22, the protocol specified a PET/CT imaging time of 60 ± 15 minutes post-dose. However, the imaging time in the study reported a range of 39 to 97 minutes with 4 subjects between 39 and 45 minutes and 9 subjects between 75 and 97 minutes. Due to the fact that the study was not designed to compare efficacy results in different imaging time intervals, the imaging time accepted for labeling is 45 to 90 minutes.

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

Yes. The proposed single intravenous dose of 4 mCi Cu-64 dotatate is appropriate for the general patient population for which the indication is being sought.

In Study RMX-18-22, subjects were administered a mean (SD) single intravenous bolus dose of 4.11 (±0.17) mCi Cu-64 dotatate. All three readers demonstrated success on the co-primary efficacy endpoints. There were only 5 subjects (8%) with observed AEs, none of them serious.

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

Renal impairment: No dedicated renal impairment studies were conducted. In Study RMX-18-22, subjects were classified using the Cockcroft-Gault (C-G) equation for renal function. Six

subjects had plasma PK samples collected. Due to bioanalytical issues with measuring Cu-64 dotatate concentrations, exposure-response analyses for efficacy and safety were not evaluated. Table 4 shows image performance stratified by renal function, however, due to the small sample sizes, the results are inconclusive. Patients with severe renal impairment were not studied.

Table 4. Sensitivity and Specificity of Individual Readers by Subject Renal Function

Renal Function	Reader 1 (%)	Reader 2 (%)	Reader 3 (%)
Normal (CL_{Cr} ≥ 90 mL/min/1.73 m^2)			
Sensitivity (n=20)	90	95	90
Specificity (n=24)	91	79	88
Mild (CL_{Cr} < 90 and ≥ 60 mL/min/1.73 m^2)			
Sensitivity (n=9)	100	100	100
Specificity (n=2)	100	100	100
Moderate (CL_{Cr} < 60 and ≥30 mL/min/1.73 m^2)			
Sensitivity (n=4)	75	50	75
Specificity (n=4)	100	75	100

Source: FDA reviewer's analysis
Abbreviations: CL_{Cr}, creatinine clearance

Hepatic impairment: No dedicated hepatic impairment studies were conducted. In Study RMX-18-22, subjects were classified using the National Cancer Institute−Organ Dysfunction Working Group criteria for hepatic function classification. Based on image performance assessment by hepatic function, no significant difference in imaging performance (Table 5) was identified between patients with normal hepatic function and mild hepatic impairment. Patients with moderate or severe hepatic impairment were not studied.

Table 5. Sensitivity and Specificity of Individual Readers by Subject Hepatic Function

Renal Function	Reader 1 (%)	Reader 2 (%)	Reader 3 (%)
Normal			
Sensitivity (n=27)	89	89	89
Specificity (n=30)	90	80	90
Mild			
Sensitivity (n=6)	100	100	100
Specificity (n=0)	ND	ND	ND

Source: FDA reviewer's analysis
Abbreviations: ND, not definable

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

Drug interaction: No dedicated drug interaction study was conducted. However, non-radioactive somatostatin analogs and Cu-64 dotatate competitively bind to SSTR2. In Study RMX-18-22, the protocol required subjects to avoid long-acting octreotide acetate depot or lanreotide within 28 days prior to study imaging and short-acting, non-depot octreotide acetate within 2 days prior to study imaging. Based on co-medication data in the study, 5 patients who had previously received somatostatin analogs followed the protocol recommendation prior to imaging. The results were all true positive, suggesting that the criteria were sufficient to provide adequate imaging performance (Table 6).

Table 6. Co-medication Information of Subjects Who Took Somatostatin Analogs in Study RMX-18-22

Subject ID	Somatostatin Analog	Reader 1	Reader 2	Reader 3
(b) (6)	Octreotide (IV PRN; ongoing)	TP	TP	TP
	Octreotide (SC Q4W; ongoing)	TP	TP	TP
	Lanreotide (IM Q4W; stopped 1 month before imaging)	TP	TP	TP
	Lanreotide (IM Q4W; stopped 1 month before imaging)	TP	TP	TP
	Lanreotide (SC Q4W; stopped 1 month before imaging)	TP	TP	TP

Source: FDA reviewer's analysis
Abbreviations: IM, intramuscular; IV, intravenous; PRN, as needed; Q4W, every 4 weeks; SC, subcutaneous; TP, true positive

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 7. Listing of Clinical Trials

Trial Identity	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Sample Size	Study Population	No. of Centers and Countries
Studies supporting efficacy and safety						
RMX-18-22	Applicant-conducted, prospective phase 3 trial evaluating imaging performance of Cu-64 dotatate PET against a reference standard	Intravenous injection of 148 MBq (4 mCi) Cu-64 dotatate	Subject-level sensitivity and specificity of Cu-64 dotatate for NET	63	42 patients with prior history of pathologically confirmed NET or suspected NET and 21 healthy volunteers	1 (U.S.)
(Pfeifer et al. 2015)	Prospective phase 2 study comparing performance of Cu-64 dotatate and In-111 pentetreotide	Intravenous injection of 202 MBq (range 183-232 MBq) Cu-64 dotatate Intravenous injection of 218 MBq (range 181-268 MBq) of In-111 pentetreotide	Comparative performance of Cu-64 dotatate and In-111 pentetreotide for NET	112	Patients with prior history of pathologically confirmed NET	1 (Denmark)
NETMedix Denmark	Applicant-conducted, retrospective re-analysis of source data collected in Pfeifer et al., 2015, evaluating imaging performance of Cu-64 dotatate PET against a reference standard (Pfeifer et al. 2015)	Intravenous injection of 202 MBq (range 183-232 MBq) Cu-64 dotatate	Patient-level sensitivity and specificity of Cu-64 dotatate for NET	112	Patients with prior history of pathologically confirmed NET	1 (Denmark)

Trial Identity	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Sample Size	Study Population	No. of Centers and Countries
Additional study supporting efficacy						
(Johnbeck et al. 2017)	Prospective phase 2 study comparing performance of Cu-64 dotatate and Ga-68 dotatoc	Intravenous injection of 200 MBq of Cu-64 dotatate Intravenous injection of 150 MBq of Ga-68 dotatoc	Comparative performance of Cu-64 dotatate and Ga-68 dotatoc for NET	59	Patients with prior history of pathologically confirmed NET	1 (Denmark)
Additional studies supporting safety						
(Pfeifer et al. 2012)	Prospective first-in-human study	Intravenous injection of 193–232 MBq of Cu-64 dotatate	Biodistribution and dosimetry	14	Patients with prior history of pathologically confirmed NET	1 (Denmark)
RMX-17-22	Applicant-conducted phase 1 dose-ranging study	Intravenous injection in 3 Cu-64 dotatate dose cohorts: 111 MBq (3 mCi), 148 MBq (4 mCi), and (185 MBq) 5 mCi	Image quality scores for each dosing cohort	12	Patients with prior history of pathologically confirmed NET	1 (U.S.)

Abbreviations: NET, neuroendocrine tumors; PET, positron emission tomography

7.2. Review Strategy

The prospective phase 3 study (Study RMX-18-22) and the re-analysis of data published in Pfeifer et al., 2015, (NETMedix Denmark Trial) were considered to provide the main support for the NDA since they were conducted by the Applicant and were accompanied by source data in the submission (Pfeifer et al. 2015). Other studies listed in Section 7.1 were reviewed for additional supportive purposes.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study RMX-18-22

Trial Design

Study RMX-18-22 was a phase 3, prospective, single-center (Excel Diagnostics and Nuclear Oncology Center in Houston), single-dose, single-arm, non-comparative clinical study. A SPA was requested by the Applicant on 4/6/2018 for this trial, and an agreement letter was sent on 5/17/2018. The primary objective of the study was to assess the imaging performance of Cu-64 dotatate PET through comparison of individual PET reader results to a SOT for each subject.

Subjects Studied and Their Baseline Characteristics

The study evaluated 42 adult patients (including 4 patients from the selected 4 mCi dose cohort of the phase 1 study, RMX-17-22) with history of confirmed NET or suspicion of NET based on histology reports, clinical symptoms and signs, or conventional, anatomical, and functional imaging modalities including, but not limited to, MRI, contrast CT, F-18 FDG PET/CT, F-18 sodium fluoride PET/CT, bone scintigraphy and In-111 pentetreotide SPECT collected within 8 weeks prior to Cu-64 dotatate PET. Of these 42 patients, 37 (88%) had a prior history of NET. The study also recruited 21 healthy adult volunteers who had no clinically relevant abnormalities as determined by a full medical history, physical examination, vital signs and clinical laboratory tests.

The Efficacy Evaluable (EE) Population included all 63 subjects as defined by the following additional criteria:

- had an established SOT, and
- were injected with Cu-64 dotatate, and
- had Cu-64 dotatate PET read results.

Of note, a single subject (b) (6) had a "Not Evaluable" result recorded for one of the PET readers. Thus, composition of the EE population (N=63) was as follows:

- patients with prior history of NET: n=37,
- patients with clinical suspicion of NET but no prior history: n=5 (1 unevaluable),
- healthy volunteers: n=21.

The 63 EE subjects also comprised the safety population for the study.

Demographic Characteristics

The median age of all enrolled subjects was 54 years (range: 25 to 82 years). The study consisted of 28 (44.4%) men and 35 (55.6%) women. The majority of subjects were white (85.7%) and not Hispanic or Latino (82.5%). African American subjects comprised 9.5% of the study population. The remaining subjects were Asian (3.2%) or other (1.6%).

Table 8. Demographics and Baseline Characteristics (Study RMX-18-22 Safety Population)

Characteristic	Overall (N = 63)
Age (years), n	
Mean (SD)	54.37 (15.65)
Median (min, max)	54.00 (25.0, 82.0)
Height (in), n	
Mean (SD)	67.67 (4.54)
Median (min, max)	68.00 (58.0, 78.7)
Weight (lb), n	
Mean (SD)	185.75 (46.70)
Median (min, max)	178.00 (114.0, 327.0)
Gender, n (%)	
Male	28 (44.4%)
Female	35 (55.6%)
Race, n (%)	
American Indian or Alaska Native	0 (0.0%)
Asian	2 (3.2%)
Black or African American	6 (9.5%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)
White	54 (85.7%)
Other	1 (1.6%)
Ethnicity, n (%)	
Hispanic or Latino	11 (17.5%)
Not Hispanic or Latino	52 (82.5%)
Unknown	0 (0.0%)
Not Reported	0 (0.0%)

Source: RMX-18-22 Study Report
Abbreviations: SD, standard deviation

Dose

A mean (SD) single intravenous bolus dose of 4.11 (±0.17) mCi Cu-64 dotatate was administered.

Protocol Deviations

PET/CT images were acquired outside of the protocol time window for 13 subjects. These deviations ranged from 6 minutes earlier to 22 minutes later than the protocol requirement of 60 ± 15 minutes (45-75 minutes). Blood draws were performed outside of the protocol time window for 7 subjects. The review team felt that these protocol deviations were unlikely to have an important impact on the safety and efficacy evaluation.

Study Endpoints

The co-primary efficacy endpoints were the subject-level sensitivity and specificity of Cu-64 dotatate PET for NET.

Image Interpretation Methodology

Cu-64 dotatate PET/CT images were interpreted independently by three nuclear medicine readers blinded to clinical information, other imaging studies, and SOT results. The readers categorized each subject as "Disease" or "No Disease" in a qualitative fashion through visual interpretation. According to the Independent Review Charter submitted as an amendment to the NDA on 4/29/20, the liver was used as a reference region to define areas of abnormal uptake. Focal activity greater than activity in the liver was considered as "Disease."

If a subject was categorized as "Disease", the reader further made a "Localized" or "Metastatic" disease classification. Per the Independent Review Charter, disease was considered localized when it was confined to a single primary site, including potential loco-regional lymph nodes.

Seven PET scans were randomly selected for the assessment of intra-reader variability. Cases selected for intra-reader variability were reintroduced to the independent reviewers not earlier than 4 weeks after the primary read.

Standard of Truth

All 21 healthy volunteers were categorized as "No Disease" after the contrast CT component of the Cu-64 dotatate PET was confirmed to be negative for suspicious lesions by an independent radiologist blinded to PET images.

One oncologist who was blinded to Cu-64 dotatate PET imaging findings established the SOT for each of the remaining 42 patients by categorizing them as "Disease" or "No Disease" based upon review of the following sources of data: available histopathology results, imaging reports (MRI, contrast CT, F-18 FDG PET/CT, F-18 sodium fluoride PET/CT, bone scintigraphy, In-111 pentetreotide SPECT, and Ga-68 dotatate PET/CT performed within 8 weeks prior to Cu-64 dotatate PET), physical examination information, and medical history including laboratory data such as chromogranin A and serotonin levels. The Applicant's Independent Review Charter included the SOT criteria shown in Table 9.

Table 9. Criteria for Standard of Truth (SOT) Determination in Study RMX-18-22

No.	SOT	Outcome
1	Confirmed histopathologically NET tumors, if not fully resected	Disease
2	At least one lesion identified by anatomical imaging (CT and/or MRI) or functional imaging ($Na^{18}F$ and/or ^{18}F-FDG and/or bone scan and/or Octreoscan) and consistent clinical data.	Disease
3	Healthy volunteers or patients with neither histological confirmation nor a lesion identified on anatomical imaging (CT and/or MRI) or functional imaging ($Na^{18}F$ and/or ^{18}F-FDG and/or bone scan and/or Octreoscan) and clinical data inconsistent for NET.	No Disease

Source: Applicant's Independent Review Charter, Table 2
Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; NET, neuroendocrine tumor

If criterion 1 was satisfied, the categorization of "Disease" was assigned without reliance on imaging and clinical information. Of note, patients with history of histologically confirmed NET could be categorized as "No Disease" if the tumor had been resected and imaging and clinical data failed to identify evidence of residual or recurrent disease.

In regard to criterion 2, clinical data from medical history and physical examination were only used to further support imaging data that identified a lesion. Clinical data was not used in isolation to confirm disease. Anatomic imaging evidence of disease was defined as a mass consistent with NET. The Independent Review Charter listed the following as evidence of disease on functional imaging:

- Functional imaging reports suggestive of metabolically active tumor/lesion on F-18 FDG PET scans. For positive lesions, non-specific inflammatory or infectious lesions should be excluded as disease. Negative F-18 FDG PET findings will not rule out NET lesion since some low grade NET lesions are not F-18 FDG avid. It is noted that F-18 FDG PET shows low or no uptake in well or moderately differentiated NET, but increases in poorly differentiated NETs. In contrast, somatostatin expression increases with increasing differentiation. This will be considered while assessing SOT based on F-18 FDG PET imaging results.
- Lesions in the skeletal system based on F-18 sodium fluoride PET/CT or bone scan.
- Lesions identified on In-111 pentetreotide SPECT imaging scan and/or Ga-68 dotatate PET/CT.

Patients categorized as "Disease" were also further classified by the SOT oncologist as "Localized" or "Metastatic" disease. Disease was considered localized when it was confined to a single primary site, including potential loco-regional lymph nodes.

Reviewer's Comments: Given that not all subjects have histopathology data, the review team considers this SOT to be more appropriately described as a composite reference standard.

Statistical Analysis Plan

Success criteria required the lower bound of the 95% confidence interval (CI) estimates for both sensitivity and specificity to exceed the specified thresholds of 70% for sensitivity and 60% for specificity in the same two out of three PET readers.

Reviewer's Comments: Using the Applicant's composite reference standard, some SOT results were assigned as positive without histopathology data. However, sensitivity and specificity are generally defined based on a histopathology truth standard. Therefore, the review team refers to 'sensitivity' as positive percent agreement (PPA) and to 'specificity' as negative percent agreement (NPA), although 'sensitivity' and 'specificity' will be displayed in the Applicant's analyses.

Patient Disposition, Data Quality, and Integrity

There was minimal missing data. The study enrolled 66 subjects including 4 subjects from the phase 1 Study RMX-17-22. Three subjects withdrew their consent prior to receiving Cu-64 dotatate. The remaining 63 subjects (59 from the phase 3 study and 4 from the phase 1 study) were injected with Cu-64 dotatate at an intended dose of 4.0 mCi and were analyzed for safety and efficacy.

Efficacy Results – Primary, Secondary, and Other Relevant Endpoints

All three readers demonstrated success on the co-primary efficacy endpoints with their lower bounds of the 95% CI for PPA (sensitivity) exceeding 70% and NPA (specificity) exceeding 60%. The PPA was 91% for all three readers, and the NPA ranged from 80 to 97% for the three readers. As described above, PPA and NPA were defined against the SOT assigned by a single oncologist. See Section 8.3 of the review for more detailed discussion of the primary efficacy results.

The secondary efficacy endpoints of the study included the majority read sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. Of the 63 dosed subjects, subject (b) (6) had a "Not Evaluable" read for Reader 1, and therefore, the total number of subjects in Table 10 is 62.

Table 10. Cu-64 Dotatate PET Majority Read Versus the SOT

		Standard of Truth		
Method of Evaluation		**Disease**	**No Disease**	**Total**
^{64}Cu-DOTATATE Scan Results	**Disease**	30	1	31
	No Disease	3	28	31
	Total	33	29	62

Source: Clinical Study Report, Table 11.4.1.2-1
Abbreviations: PET, positron emission tomography; SOT, standard of truth

Reviewer's comments: The majority read data displayed in Table 10 above include three false negative subjects. The NDA contains an "Oncologist Note to File" in which the Applicant retrospectively requested the oncologist making the SOT determination to change the initial SOT assessment of positive for NET disease to negative for NET disease for these three subjects, essentially converting the three false negatives to 'true negatives'. The review team disregarded this post-hoc analysis. The above Table 10 as well as primary analysis results in this section and Section 8.3 reflect the original SOT determined by the study oncologist.

In the original SOT determination presented in Table 10, four patients who previously had their NET completely resected and had no evidence of recurrence at the time of Study-RMX-18-22 were categorized as disease negative.

In a secondary analysis, majority reads for classification of localized versus metastatic disease were analyzed by the Applicant. Of the 30 true positive patients, two patients were correctly classified by PET majority read as localized and 28 patients were correctly classified as metastatic when compared to the SOT classification. The three false negative patients had a localized SOT classification.

A tertiary analysis of inter-reader reproducibility conducted by the Applicant yielded an overall Fleiss Kappa of 0.76 (95% CI, 0.62 ,0.91). The Applicant's analysis of intra-reader reproducibility demonstrated readers 1 and 2 to completely agree with their prior reads on 7 random PET scans. The third reader showed agreement on 5 of 7 repeated PET reads.

Additional Analyses Conducted on the Individual Trial

Subgroup analyses on the primary efficacy endpoints of sensitivity and specificity by age, gender, and race were performed by the Applicant. Results are shown in Table 11, Table 12, and Table 13 below. Overall there are no appreciable differences among sex, race, and age subgroups.

Table 11. Individual Reader Results by Age

Reader Parameter	<60 Years N=40	60 to 75 Years N=15	>75 Years N=8
Reader 1			
Sensitivity (95% CI)	0.9286 (0.6853, 0.9873)	0.9286 (0.6853, 0.9873)	0.8000 (0.3755, 0.9638)
Specificity (95% CI)	0.9600 (0.8046, 0.9929)	1.0000 (0.2065, 1.0000)	1.0000 (0.4385, 1.0000)
Reader 2			
Sensitivity (95% CI)	1.0000 (0.7847, 1.0000)	0.8571 (0.6006, 0.9599)	0.8000 (0.3755, 0.9638)
Specificity (95% CI)	0.8077 (0.6212, 0.9149)	1.0000 (0.2065, 1.0000)	0.6667 (0.2077, 0.9385)
Reader 3			
Sensitivity (95% CI)	0.9286 (0.6853, 0.9873)	0.9286 (0.6853, 0.9873)	0.8000 (0.3755, 0.9638)
Specificity (95% CI)	0.8846 (0.7102, 0.9600)	1.0000 (0.2065, 1.0000)	1.0000 (0.4385, 1.0000)

Source: Response to Information Request (SN10, dated 4/9/20)
Abbreviations: CI, confidence interval

Table 12. Individual Reader Results by Gender

Reader Parameter	Female N=35	Male N=28
Reader 1		
Sensitivity (95% CI)	0.8571 (0.6006, 0.9599)	0.9474 (0.7536, 0.9906)
Specificity (95% CI)	0.9500 (0.7639, 0.9911)	1.0000 (0.7009, 1.0000)
Reader 2		
Sensitivity (95% CI)	0.7857 (0.5241, 0.9243)	1.0000 (0.8318, 1.0000)
Specificity (95% CI)	0.7619 (0.5491, 0.8937)	0.8889 (0.5650, 0.9801)
Reader 3		
Sensitivity (95% CI)	0.8571 (0.6006, 0.9599)	0.9474 (0.7536, 0.9906)
Specificity (95% CI)	0.9524 (0.7733, 0.9915)	0.7778 (0.4526, 0.9368)

Source: Response to Information Request (SN10, dated 4/9/20)
Abbreviations: CI, confidence interval

Table 13. Individual Reader Results by Race

Reader Parameter	White N=54	Non-white N=9
Reader 1		
Sensitivity (95% CI)	0.9259 (0.7663, 0.9794)	0.8333 (0.4365, 0.9699)
Specificity (95% CI)	0.9615 (0.8111, 0.9932)	1.0000 (0.4385, 1.0000)
Reader 2		
Sensitivity (95% CI)	0.9630 (0.8172, 0.9934)	0.6667 (0.3000, 0.9032)
Specificity (95% CI)	0.7778 (0.5924, 0.8939)	1.0000 (0.4385, 1.0000)
Reader 3		
Sensitivity (95% CI)	0.9259 (0.7663, 0.9794)	0.8333 (0.4365, 0.9699)
Specificity (95% CI)	0.9259 (0.7663, 0.9794)	0.6667 (0.2077, 0.9385)

Source: Response to Information Request (SN10, dated 4/9/20)
Abbreviations: CI, confidence interval

The review team noted that healthy volunteers, all 21 of whom were negative by both the SOT and Cu-64 dotatate PET majority read, are not representative of the population of intended use. Aside from heathy volunteers, an additional 8 patients were SOT negative, including all 4 evaluable patients with suspicion of NET but no known history and 4 patients with prior history of confirmed NET. Of these patients, the Cu-64 dotatate PET majority read was true negative for 7 (including all 4 evaluable patients with suspicion of NET but no known history) and false positive for 1 patient. While these results suggest high negative percent agreement within this clinically relevant subgroup, the small sample size limits its estimation.

8.1.2. Published Study (Pfeifer et al., 2015)

Trial Design

A publication by Pfeifer et al., 2015, describes a prospective, single-center study that was performed to compare on a head-to-head basis the performance of Cu-64 dotatate PET (183 to232 MBq) and In-111 pentetreotide SPECT in 112 patients with a history of pathologically confirmed gastroenteropancreatic or pulmonary NETs.

All patients were being referred for standard-of-care evaluation of residual disease and underwent all of the following baseline imaging studies:

- Cu-64 dotatate PET/CT scan,
- In-111 pentetreotide SPECT/CT,
- diagnostic CT scan (using contrast unless contraindicated).

Patients were followed up for 42 to 60 months for evaluation of discrepant imaging findings through additional imaging and/or biopsy.

Demographic Characteristics

All 112 patients were studied at a single site in Demark. The study group consisted of 63 (56%) men and 49 (44%) women with a mean age of 62 years (range 30 to 84 years). While all patients had a history of histologically verified neuroendocrine tumor, 52 (46%) patients had their primary tumor removed, while the remaining 60 patients (54%) did not.

Image Interpretation Methodology

Cu-64 dotatate PET/CT and In-111 pentetreotide SPECT/CT scans were analyzed separately by two different teams, each consisting of two experienced interpreters. The PET/CT team and the SPECT/CT team remained the same throughout the study and did not have access to other clinical information including patient history. The two teams were also blinded to the images and readings of the other team. Diagnostic CT scans were evaluated by a separate experienced radiologist blinded to both PET/CT and SPECT/CT images.

The review team referred to the sample case report form from the related NETMedix Denmark Trial for the image interpretation methodology used in the publication. Based on the submitted sample case report form, each baseline scan (Cu-64 dotatate PET, In-111 Octreotide SPECT, diagnostic CT scan) was rated as positive or negative with the site of tumor involvement as a comment for each scan.

Standard of Truth

The review team referred to the sample case report form from the related NETMedix Denmark Trial for information on the truth standard. Concordant results between baseline Cu-64dotatate PET/CT and In-111 pentetreotide SPECT/CT were considered true positive while discrepant results were compared to a composite reference standard including the baseline diagnostic CT as well as follow-up histopathology and imaging collected over a period of 42 to 60 months. Although little information was supplied in the publication regarding the composite reference standard, more details are available through the re-analysis conducted by the Applicant in the NETMedix Denmark trial, as described later in Section 8.1.3 of this review.

Efficacy Results

All 112 patients underwent Cu-64 dotatate PET/CT, In-111 pentetreotide SPECT/CT scans, and contrast diagnostic CT. In 100 of 112 patients, residual or recurrent disease was established by the SOT. The remaining 12 patients were classified as negative for disease.

Eighty-seven patients were congruently positive on both Cu-64 dotatate PET and In-111 pentetreotide SPECT scans. Ten patients with proven residual or recurrent disease were identified only by Cu-64 dotatate PET, leading to 97 true-positive Cu-64 dotatate PET cases. Cu-64 dotatate PET was false-negative in three patients. No false-positive results were seen for either Cu-64 dotatate PET or In-111 pentetreotide SPECT on a per patient basis.

A comparison of Cu-64 dotatate PET results against the SOT appears below, with FDA analysis yielding sensitivity of 97% (95% CI: 91 ,99%) and specificity of 100% (95% CI: 74 ,100%).

Table 14. Cu-64 Dotatate PET vs. SOT Results in Pfeifer et al., 2015

Parameter	SOT Positive	SOT Negative	Total
Cu-64 DOTATATE PET Positive	TP=97	FP=0	97
Cu-64 DOTATE PET Negative	FN=3	TN=12	15
Total	100	12	112

Source: Compiled from descriptions in Pfeifer et al., 2015.
Abbreviations: FN, false negative; FP, false positive; PET, positron emission tomography; SOT, standard of truth; TN, true negative; TP, true positive

Reviewer's comments: Since the SOT in the study was largely based on imaging agreement, the review team regards PPA and NPA as more appropriate terms than sensitivity and specificity, respectively, to describe performance characteristics in this trial.

The authors noted that over twice as many lesions were detected with Cu-64 dotatate than with In-111 pentetreotide. On an organ-level, the authors reported that 58 organs were identified as positive with Cu-64 dotatate PET but not with In-111 pentetreotide SPECT, with 46 (79%) of these discrepant organs determined to be true-positive on PET through follow-up imaging and histopathology collected over 42 to 60 months as the SOT.

8.1.3. NETMedix Denmark Study

Study Design

This study conducted by the Applicant was a retrospective re-analysis of the data collected for the Pfeifer et al., 2015, publication, with particular focus on evaluating imaging performance of Cu-64 dotatate PET against a SOT rather than comparison to In-111 pentetreotide SPECT. All 112 patients in the Pfeifer et al., 2015, study were included. Of note, the re-analysis did not involve re-reading of any imaging. Rather, it focused on retrospective verification of the SOT through review of source data that were only summarized in the original Pfeifer et al., 2015, publication. The re-analysis also added safety findings that were not mentioned in the original publication.

Efficacy Endpoints

The co-primary efficacy endpoints of the study were the patient-level sensitivity and specificity of Cu-64 dotatate against the SOT.

Standard of Truth

As noted for Pfeifer et al., 2015, each of the 112 patients underwent baseline Cu-64 dotatate PET/CT scan, In-111 pentetreotide SPECT/CT, diagnostic CT scan (using contrast unless contraindicated). These three required imaging studies were referred to as "reference scans" by the Applicant. Reference scan reads from the PET team, SPECT team, and CT radiologist were identical to those from Pfeifer et al., 2015. The study used a combination of agreement of baseline reference scan results as well as follow-up for discrepant cases that variably incorporated histopathology and/or additional imaging such as CT, MRI, US, In-111 pentetreotide SPECT, Ga-68 dotatoc PET, and F-18 FDG PET (Pfeifer et al. 2015).

In the clinical study report, the Applicant listed the following description of the SOT:

1. A patient who is negative on both reference diagnostic CT and In-111 pentetreotide SPECT/CT is negative.
2. A patient who is positive on either of the reference scans is positive.
3. A patient whose tumor was confirmed as NET via biopsy, surgical resection, follow-up imaging using SSTR-based imaging modalities (other than Cu-64 dotatate), CT, MR or US is positive.
4. A patient is considered true positive and no further follow-up was needed if both reference Cu-64 dotatate PET and In-111 pentetreotide SPECT are positive.
5. Patients with discrepant findings on reference Cu-64 dotatate PET and In-111 pentetreotide SPECT were considered positive if NET was confirmed during follow-up via biopsy, another somatostatin receptor imaging modality (i.e., In-111 pentetreotide SPECT), or additional imaging (CT, MR or US). Patients with discrepant findings were always positive on Cu-64 dotatate PET and negative on In-111 pentetreotide SPECT.

Reviewer's comments: The SOT was clarified through discussion at the NDA mid-cycle review meeting. In 89 of 112 patients (79%), reference Cu-64 dotatate PET and reference In-111 pentetreotide SPECT were both positive. Based only on this agreement in these 89 patients, the SOT was considered positive, and thereby Cu-64 dotatate PET was considered true positive. In an additional five patients, reference Cu-64 dotatate PET and reference diagnostic CT were positive while reference In-111 pentetreotide SPECT was negative, leading to a SOT determination of positive (true positive Cu-64 dotatate PET). In a single patient, reference Cu-64 dotatate PET and reference In-111 pentetreotide SPECT were negative while reference diagnostic CT was positive, leading to a SOT determination of positive (false negative Cu-64 dotatate PET).

Of the remaining 17 patients, 12 were negative by all three reference scans and five were positive only on Cu-64 dotatate PET. Narratives that detailed follow-up for all 17 of these patients were submitted by the Applicant. For the five patients who were positive only on reference Cu-64 dotatate PET (case # (b) (6)), subsequent biopsy/resection and/or additional follow-up imaging such as diagnostic CT, In-111 pentetreotide SPECT, or Ga-68 dotatoc PET at later dates lead to a final positive SOT determination by the Applicant (Cu-64 dotatate PET true positive). The review team finds the SOT determination for these five patients to be reasonable.

The 12 patients who were negative on all three reference scans, including Cu-64 dotatate PET, had all undergone treatment for NET such as surgery, radiofrequency ablation, or peptide receptor radionuclide therapy. The submitted narratives for these patients detailed several years of follow-up including biopsies and/or imaging that variably included MRI, CT, F-18 FDG PET, In-111 pentetreotide SPECT, and Ga-68 dotatoc PET. In four of the 12 patients (cases # (b) (6)) findings were consistently negative for NET. In another patient, (case (b) (6)) only an unrelated primary tumor (hepatocellular carcinoma) was identified. In the maining seven of the 12 patients (cases # (b) (6)), years of negative follow-up subsequently led to new findings suspicious for tumor recurrence/metastasis that were not previously documented. The SOT for all 12 patients was determined to be negative by the Applicant (Cu-64 dotatate PET true negative). The review team finds the SOT determination for these 12 patients to be reasonable.

Statistical Analysis Plan

The following two hypotheses were tested relative to the patient-level co-primary endpoints:

- H_{a0}: Sensitivity ≤ 80% vs H_{a1}: Sensitivity > 80%
- H_{b0}: Specificity ≤ 60% vs H_{b1}: Specificity > 60%

Each hypothesis was tested at the one-sided $\alpha = 0.025$ level of significance.

Reviewer's comments: Given that the original Pfeifer et al., 2015, study was re-analyzed to compare against pre-specified thresholds for sensitivity and specificity, the scientific validity of the NETMedix Denmark Study relies on the appropriateness of retrospective verification of the SOT (composite reference standard) since the images were not re-read (Pfeifer et al. 2015).

Efficacy Results

Table 15. NETMedix Denmark Study Results for Cu-64 Dotatate PET vs. SOT

		Standard of Truth		
Method of Evaluation		**Disease**	**No Disease**	**Total**
^{64}Cu-DOTATATE Scan Results	**Disease**	99	0	99
	No Disease	1	12	13
	Total	100	12	112

Source: NETMedix Denmark Study CSR
Abbreviations: PET, positron emission tomography; SOT, standard of truth

Reviewer's comments: Compared to the original study (Pfeifer et al., 2015), two false negative patients were reclassified as true positives. In the Applicant's response to an information request, they explained these two cases had been erroneously classified as Cu-64 dotatate PET negative in the original Pfeifer et al., 2015, publication due to errors for case 79 and 84 when transferring the data. The Applicant stated that their reclassification accurately reflected the Cu-64 dotatate PET read results captured on the original case report forms. The Applicant's reclassification of these two patients has minimal impact on sensitivity and no impact on specificity (Pfeifer et al. 2015).

Table 16. NETMedix Denmark Study Summary Statistics for Cu-64 Dotatate PET vs. SOT

		Summary Statistics
Parameter	**Estimate**	**95% CI**
Sensitivity[a]	0.9900	(0.9455, 0.9982)
False Negative Rate	0.0100	(0.0018, 0.0545)
Specificity[b]	1.0000	(0.7575, 1.0000)
False Positive Rate	0.0000	(0.0000, 0.2425)

Source: NETMedix Denmark Trial CSR
Abbreviations: CI, confidence interval; PET, positron emission tomography; SOT, standard of truth

Reviewer's comments: As in Pfeifer et al., 2015, since the SOT was largely based on imaging agreement, the review team regards positive percent agreement and negative percent agreement as more appropriate terms than sensitivity and specificity, respectively, to describe performance characteristics in this trial (Pfeifer et al. 2015).

8.1.4. Published Study (Johnbeck et al., 2017)

This study compared on a head-to-head basis the imaging performance of Cu-64 dotatate to that of Ga-68 dotatoc in patients with NET.

Sixty patients with NET, of which 59 were evaluable, were prospectively enrolled in the study at Rigshospitalet, Copenhagen. One patient was omitted from the study at the quality check due to subcutaneously injected Ga-68 dotatoc. The remaining 59 patients were scanned with both Cu-64 dotatate PET/CT and Ga-68 dotatoc PET/CT. The CT scan performed in conjunction with the Cu-64 dotatate PET utilized intravenous contrast and was of diagnostic quality while the CT

scan performed in conjunction with the Ga-68 dotatoc PET did not utilize intravenous contrast and was of non-diagnostic quality (low-dose 120 kV, effective 40 mAs).

A nuclear medicine specialist and a radiologist evaluated by consensus both PET scans simultaneously for each patient. This method would be expected to mitigate the difference in CT quality between the scans, at least in part. All lesions on the Cu-64 dotatate PET/CT and Ga-68 dotatoc PET/CT scans were compared, and discordant lesions were noted for each of the scans. Discordant lesions were compared to a reference standard of all available later imaging (Ga-68 dotatoc PET, CT, and MRI) collected over at least 30 months of follow up in order to classify the lesions as true positive or false positive. The degree of blinding during collection of PET reads and reference standard results was not specified.

A total of 701 lesions (in 37 of the 59 patients) were concordantly detected on both Cu-64 dotatate PET and Ga-68 dotatoc PET scans while an additional 68 lesions were found by only one of the scans. Cu-64 dotatate PET showed 42 lesions not found on Ga-68 dotatoc PET, of which 33 were found to be true positive on follow up. Ga-68 dotatoc PET showed 26 lesions not found on Cu-64 dotatate PET, of which seven were found to be true positive on follow up. False positives were mainly lymph nodes.

On a patient-level, additional true positive lesions were found by Cu-64 dotatate PET and Ga-68 dotatoc PET in 13 and 3 patients, respectively. However, all patients with additional lesions also had concordant lesions found by both scans. Thus, the authors concluded that patient-level diagnostic performance was similar for Cu-64 dotatate PET and Ga-68 dotatoc PET with sensitivity of 100 % (95% CI; 93 ,100 %), specificity 90% (95% CI; 56, 100 %), positive predictive value 98% (95% CI; 90, 100%), and negative predictive value of 100% (95% CI; 66, 100%). However, more true positive lesions were revealed by Cu-64 dotatate PET compared to Ga-68 dotatoc PET.

Given the limitations of the study (e.g., difference in CT quality between Cu-64 dotatate PET and Ga-68 dotatoc PET, unspecified blinding, limited composite reference information) and lack of submitted source data for verification of results, the review team considers this publication as only supportive of the efficacy results determined in Study RMX-18-22 and the NETMedix Denmark Study.

8.1.5. Integrated Assessment of Efficacy Across Trials

Study RMX-18-22 and the NETMedix Denmark Study provide the primary evidence of efficacy for this application since submitted source data were included. Of these , Study RMX-18-22 provides the stronger level of evidence, as the prospective protocol was agreed upon with FDA under a SPA and incorporated multiple independent PET readers as well as pre-specified success criteria. While the SOT for each study was weakened by incorporation of agreement with baseline conventional imaging, this element dominated the reference standard of the NETMedix Denmark Study. Study RMX-18-22, on the other hand, contained an important proportion of patients with histopathology in the SOT, as further explored in Section 8.3 of this review.

Both Study RMX-18-22 and the NETMedix Denmark Study showed similar imaging performance for NET. Although the NETMedix Denmark Study was of an overall weaker design, it provides supportive evidence of Cu-64 dotatate PET performance beyond the single study center of Study RMX-18-22.

A design weakness unique to Study RMX-18-22 was incorporation of healthy volunteers who do not reflect the population of intended use. However, as discussed above, similar high negative percent agreement as was demonstrated in the healthy volunteers was suggested in the small group of study patients who had a history or suspicion of NET but were determined to be SOT negative. Although not ideal, use of healthy volunteers to aid estimation of negative percent agreement in Study RMX-18-22 is reasonable given the orphan drug context. Of note, the remainder of the studies reviewed for efficacy, including the NETMedix Denmark Study, exclusively evaluated patients with known history of NET.

Out of all studies reviewed for efficacy, only Study RMX-18-22 included patients without a history of NET who were suspected of a possible NET diagnosis. This group was limited to only four evaluable patients in Study RMX-18-22, all of whom were negative for disease by both the SOT and consensus Cu-64 dotatate PET read. Of note, high rates of SSTR PET negativity in such suspected NET patients has been reported in the literature (Graham et al. 2017; Hope et al. 2018). Given the extremely limited data in this application for this patient group and the uncertain clinical meaningfulness of a negative SSTR PET in these patients in general, a statement in the Warnings and Precautions section of labeling will caution that a negative Cu-64 dotatate PET scan might not rule out disease in patients who do not have a history of NET.

8.2. Review of Safety

8.2.1. Safety Review Approach

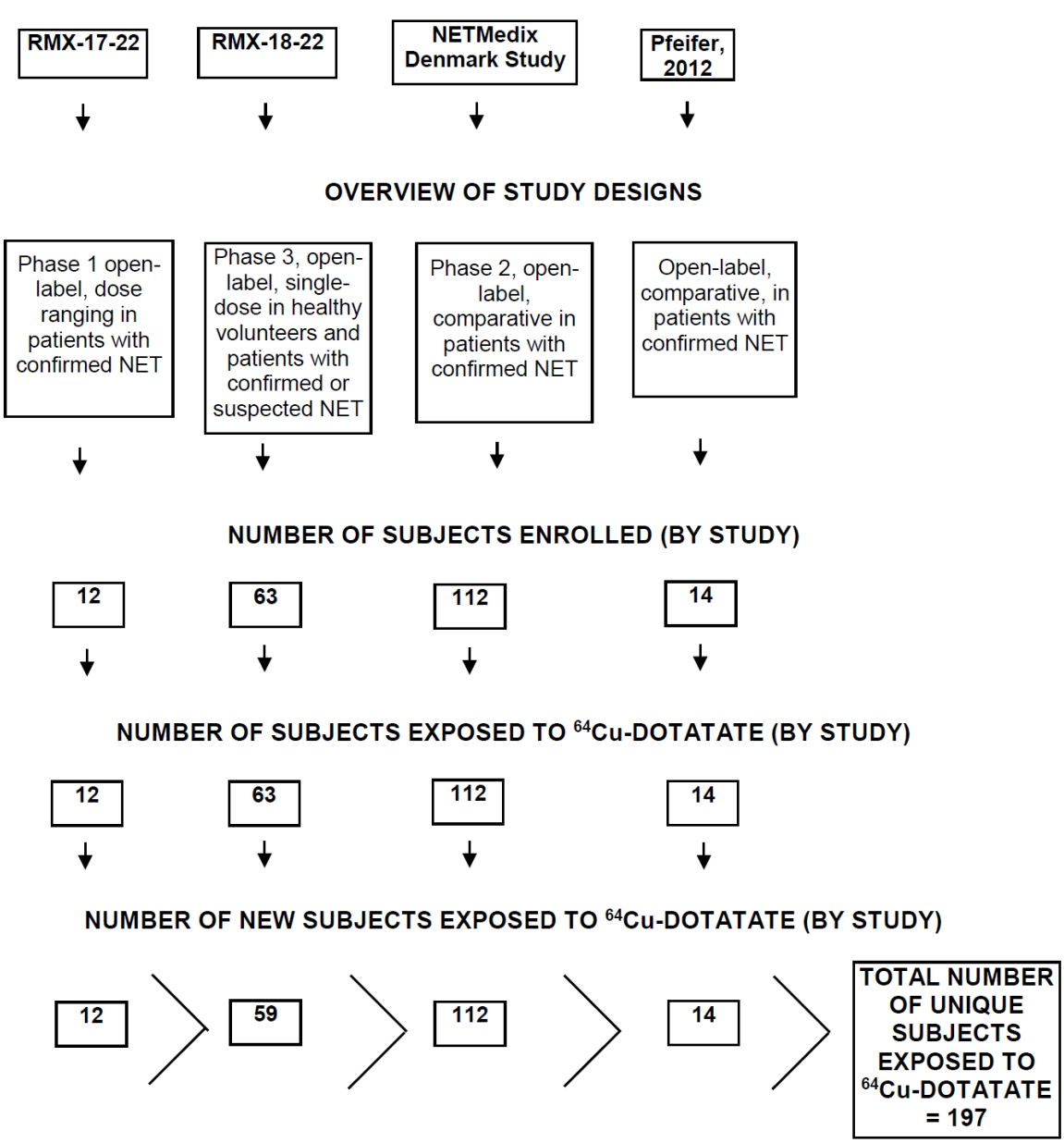
Safety source data were available from three Applicant-conducted studies, dose-ranging Study RMX-17-22, phase 3 Study RMX-18-22, and reanalysis of data from Pfeifer et al., 2015, in the NETMedix Denmark Study (Pfeifer et al. 2015). The Pfeifer et al., 2012, publication also contained a summary of safety results (Pfeifer et al. 2012). The Johnbeck et al., 2017 publication did not mention safety monitoring or safety results (Johnbeck et al. 2017). The review team further conducted a literature search and identified a published abstract relevant to safety evaluation (Kjaer et al. 2019).

8.2.2. Review of the Safety Database

Overall Exposure

The overall extent of exposure to Cu-64 dotatate across the clinical trials and literature-based sources submitted by the Applicant are summarized in Figure 3:

Figure 3. Applicant's Submitted Safety Database



Source: Applicant's Summary of Clinical Safety, Figure 2.7.4-1
Abbreviations: NET, neuroendocrine tumor

Four subjects from Study RMX-17-22 participated in Study RMX-18-22. Therefore, they were not included as the total number of "new" subjects exposed to Cu-64 dotatate in Figure 3. The total number of unique subjects exposed to Cu-64 dotatate was 197. All studies were single-dose; therefore, there were 197 injections.

Of the 197 subject exposures to Cu-64 dotatate in the four studies contributing to the safety database, all were adults (≥18 years of age). An overall summary of demographic characteristics for the safety database is presented in Table 17 below. It should be noted that racial or ethnic

characteristics are not expected to affect binding characteristics or diagnostic performance of radiopharmaceuticals that target SSTR.

Table 17. Overall Demographic Profile of Subjects Exposed to Cu-64 Dotatate: by Study, Age, Sex, and Race

Demographic Parameter	RMX-17-22 N=12	RMX-18-22 N=63[a]	NETMedix Denmark Study N=112	Pfeifer, 2012 N=14
Age (years)				
Mean ± SD	NA	54.37 ± 15.65	61.6 ± 10.85	NA
Range	44 - 83	25 - 82	30 - 84	40 – 81
Sex, N (%)				
Female	5 (41.7%)	35 (55.6%)	49 (43.8%)	4 (28.6%)
Male	7 (58.3%)	28 (44.4%)	63 (56.3%)	10 (71.4%)
Race, N (%)				
White/Caucasian	12 (100.0%)	54 (85.7%)	NA	NA
Black/African American	0	6 (9.5%)		
Hispanic/Latino	0	0		
Asian	0	2 (3.2%)		
American Indian/ Alaska Native	0	0		
Other	0	1 (1.6%)[b]		

Source: Study RMX-17-22 CSR, Table 11.2-1; Study RMX-18-22 CSR, Table 11.2-1; NETMedix Denmark Study CSR, Table 1; Pfeifer et al., 2012, Table 1 (Pfeifer et al. 2012)
[a] Four subjects from Study RMX-17-22 are included as part of the total safety population for Study RMX-18-22
[b] Subject (b) (6) had a race of other-Latino recorded in error. This subject's race should have been set to missing and therefore the percentage of subjects with a race of Other would be 0% rather than 1.6% (n=1)
Abbreviations: NA, not available; SD, standard deviation

Adequacy of the Safety Database

Since the proposed dosing regimen of Cu-64 dotatate is single administration and in microdose range, the safety database is considered adequate. Dotatate mass dose administered in Study RMX-17-22 ranged from 18 to 42.6 micrograms and in Study RMX-18-22 ranged from 8.5 to38.3 micrograms.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Detailed safety monitoring was conducted by the Applicant in Study RMX-18-22 and Study RMX-17-22, as discussed below. While summary safety results were available from the NETMedix Denmark Study and Pfeifer et al., 2012, the safety monitoring measures were not described in detail (Pfeifer et al. 2012). As such, Study RMX-18-22 and Study RMX-17-22 provide primary support for safety analysis.

Collection of Adverse Events

In Study RMX-18-22 and Study RMX-17-22, observed or patient reported early AEs were assessed within 1 hour before and within 2 hours after Cu-64 dotatate administration. Follow

up phone calls were conducted to collect delayed AEs at 24 hours and 48 hours after Cu-64 dotatate administration.

Vital Signs, Electrocardiogram, and Other Routine Clinical Tests

In Study RMX-18-22, vital signs were measured within 30 minutes before and up to 1 hour after administration of Cu-64 dotatate. In Study RMX-17-22, vital signs were measured within 30 minutes before and at 5 minutes, 10 minutes, 30 minutes, and 60 minutes after administration of Cu-64 dotatate as well as at study discharge.

In Study RMX-18-22 and Study RMX-17-22, all subjects underwent continuous electrocardiogram (ECG) recording at least 15 minutes prior to administration of Cu-64 dotatate and continuing for at least 30 minutes after administration. In addition, a 12-lead static ECG was performed within 60 minutes before and within 60 minutes following Cu-64 dotatate administration. All the ECG data were collected in digital format, analyzed and reviewed (with manual over-read) by an independent physician to determine if they were normal or abnormal and if abnormal, whether clinically significant or not significant.

In Study RMX-18-22 and Study RMX-17-22, a blood sample was collected within 30 minutes before the injection, within 2 hours post Cu-64 dotatate administration, and 1 to 2 days after PET to assess clinical chemistry and hematology.

8.2.4. Safety Results

Deaths

No death was reported in the safety database.

Serious Adverse Events

No serious AE was reported in the safety database.

Dropouts and/or Discontinuations Due to Adverse Effects

No subject discontinued study drug due to a treatment-emergent AE in any study in the development program.

Significant Adverse Events

No adverse events were considered to be of particular clinical importance.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant originally reported that no adverse events were considered definitely related, probably related, or possibly related to Cu-64 dotatate in Study RMX-17-22 or Study RMX-18-22. As discussed below, additional details were requested from the Applicant to allow more focused evaluation of the timing and potential causality of the adverse events.

In Study RMX-17-22, 4 adverse events were reported by the Applicant in three patients, as listed in Table 18.

Table 18. Patients Reporting Treatment-Emergent Adverse Events in Study RMX-17-22

Subject ID	Dose (mCi)	Number of AE's	Adverse Event(s)
(b) (6)	4.0	1	Flushing
	4.0	1	Syncope
	5.0	2	Headache, neuropathy

Source: Study RMX-17-22 CSR, Listing 16.2.7
Abbreviations: AE, adverse event

The headache and flushing events were reported during the PET visit. Syncope and neuropathy events were reported at a 24-hour follow up phone call. The syncope event was classified as moderate in severity while the other events were mild in severity. All events resolved without further intervention.

Reviewer's comments: An information request was sent to the Applicant requesting additional details of these adverse events.

For subject (b) (6) who experienced flushing, the Applicant explained that the subject experienced flushing for 3 minutes, starting 1 minute after the injection of study drug and then recovered without any intervention. As per medical history, the subject experienced flushing in the past due to carcinoid syndrome, therefore this flushing was assessed a probably not related to the study drug. Given that the event occurred immediately after injection of Cu-64 dotatate, the review team considered it to be reasonably related to study drug and therefore classified it as an adverse reaction (AR).

For subject (b) (6) who experienced syncope, the Applicant explained that, based on source documents syncope occurred 5 to 7 hours after the injection (exact time is not known)and was attributed to dehydration. As per the source document the subject had Lasix 40 mg IV in the morning of the investigational procedure for renal scan and urinated several times during the day while not keeping up with hydration. The review team agreed with the Applicant's assessment that this event was unlikely to have been related to Cu-64 dotatate. Through the information request, it was clarified that subject (b) (6) also experienced "transient generalized rash" approximately 5 to 7 hours after Cu-64 dotatate administration. This event was mild in severity and resolved spontaneously after a few hours. It was attributed by the Applicant to the subject's known history of flushing related to carcinoid syndrome. The review team again agreed with the Applicant's assessment that this event was unlikely to have been related to Cu-64 dotatate.

For subject (b) (6) who experienced headache and neuropathy, the Applicant clarified that headache was present before Cu-64 dotatate administration and was unchanged after injection. Regarding the neuropathy event, the subject reported worsening of pre-existing diabetic neuropathy at the 24-hour phone call. The subject had a recent history of waxing and waning of the neuropathy prior to Cu-64 dotatate administration. The review team agreed with the Applicant's assessment that both of these events were unlikely to have been related to Cu-64 dotatate.

In the Study RMX-18-22, the Applicant reported five patients who experienced nine adverse events, as shown in Table 19. Of these five patients, two patients with syncope and flushing were from Study RMX-17-22 (b) (6) Adverse events that were moderate in severity included syncope and hypertension. The other adverse events were all classified as mild in severity. No adverse events occurred in healthy volunteers.

Table 19. Subjects Reporting Treatment-Emergent Adverse Events in Study RMX-18-22

Subject ID	Number of AE's	Adverse Event(s)	Severity
(b) (6)	1	Syncope	Moderate
	1	Flushing	Mild
	3	Headache Vomiting (2 episodes)	Mild Mild
	2	Vomiting Hypertension	Mild Moderate
	2	Nausea Melanoderma	Mild Mild

Source: Study RMX-18-22 CSR, Data Listing 7
* Subjects (b) (6) were included from Study RMX-17-22
Abbreviations: AE, adverse event

Reviewer's comments: An information request was sent to the Applicant requesting additional details of these adverse events.

For subject (b) (6) who experienced vomiting and hypertension:

1) Regarding the vomiting event, the applicant explained that the subject experienced vomiting one minute after the injection of study drug. Vomiting was attributed to stress

experienced by the subject during the procedure. Given that the vomiting event occurred immediately after injection of Cu-64 dotatate, the review team considered it to be reasonably related to study drug and therefore classified it as an AR.

2) Regarding the hypertension event, the Applicant clarified that the subject had a history of treated hypertension as well increased blood pressure during imaging procedures related to white coat syndrome. The hypertension event was reported as occurring 4 minutes after Cu-64 dotatate administration. Given the history and the occurrence of the hypertension closely after the episode of vomiting, the review team agreed with the Applicant that the hypertension event was not likely related to Cu-64 dotatate.

For subject (b) (6) *who experienced nausea and melanoderma:*

1) Regarding the nausea event, the Applicant stated that it started 1 minute after study drug injection, lasted for 8 minutes, resolved without any intervention, and was attributed to stress experienced by the subject during the procedure. Given that the nausea event occurred immediately after injection of Cu-64 dotatate, the review team considered it to be reasonably related to study drug and therefore classified it as an AR.

2) Regarding the melanoderma event, the Applicant stated, the subject noticed 15-20 black spots about 1-3 mm on the left palm without itching, pain or redness, the day after the study drug administration. The black spots decreased in size to 1 mm after 3 days and resolved without intervention. The subject stated that he had similar black spots in the past with the use of silver nitrate., The Applicant assessed this event as probably not related to study drug and the review team agreed.

For subject (b) (6) *who experienced headache and two episodes of vomiting:*

1) Regarding the headache event, the Applicant stated that the subject has history of migraine since (b) (6) *and experienced headache (6/10) for 10 minutes, starting 90 minutes after the injection of study drug and recovered without intervention. The Applicant assessed this headache as probably not related to study drug and the review team agreed.*

2) Regarding the two episodes of vomiting, the Applicant clarified that they occurred 6 hours and 8 hours after the injection of Cu-64 dotatate. The Applicant further stated their belief that the vomiting events were related to the above presumed migraine rather than study drug. The review team agreed with the Applicant's assessment.

Altogether, the review team determined that three patients experienced three mild ARs of flushing, nausea, and vomiting in studies RMX-17-22 and RMX-18-22.

In the study by Pfeifer et al., 2012, four out of 14 patients were reported to experience self-limited nausea of seconds to a few minutes duration immediately after injection of Cu-64 dotatate. The authors attributed these events to the somatostatin analog contained in the tracer. There were no other adverse or pharmacologic effects observed. The authors also

mentioned that no significant changes in vital signs were observed. The mean ± SD of the administered mass of Cu-64 dotatate administered in this study was 33.9±1.7 ng (range, 31.7 to 38ng). Thus, the numerically higher reporting rate of nausea in this study relative to the remainder of the safety database is not explained by the administered mass dose of drug. (Pfeifer et al. 2012).

The NETMedix Denmark Study report included safety data from the 112 patients cited in the published report by Pfeifer et al. (2015). The report stated that adverse events were monitored during the study as part of routine clinical practice and that none were observed.

Laboratory Findings

In Study RMX-18-22 and Study RMX-17-22, blood samples for laboratory evaluation were collected 30 minutes before injection, 120 minutes after injection, and at the Day 1 to 2 post-injection follow-up. No clinically important changes in serum chemistry or hematology values were found between baseline and follow-up collections.

Vital Signs

In Study RMX-18-22 and Study RMX-17-22, there were no clinically important changes from baseline in vital signs occurred at 5-, 10-, 30-, or 60-minutes post-injection or at discharge.

ECGs

In Study RMX-18-22 and Study RMX-17-22, there were no shifts observed in ECG parameters from baseline to 1-hour post-injection of Cu-64 dotatate.

QT

A formal QT clinical study was not performed for this single administration microdose drug and no study was needed.

Immunogenicity

Immunogenicity evaluation was not needed and was not performed for this single administration microdose drug.

8.2.5. Analysis of Submission-Specific Safety Issues

Cu-64 is not a pure positron emitter. Cu-64 decays with a half-life of 12.7 hours by 17.6% positron emission to 64 Ni, 38.5% by beta decay to 64 Zn, 43.8% by electron capture to 64 Ni, and 0.475% gamma radiation/internal conversion. With positron emission representing only a small fraction of decay, the majority of emission does not contribute to PET imaging but does add to the overall absorbed radiation dose. However, the relatively long half-life of Cu-64 balances the low fraction of positron emission, at least in part, when considering the number of counts needed for PET imaging.

The review team considered these issues when evaluating the potential radiation risk associated with Cu-64 dotatate. Based on the phase 1 biodistribution study (Pfeifer et al. 2012), calculated radiation exposure estimates in humans yielded an effective dose of 6.3 mSv for an injected activity of 200 MBq (5.3 mCi) of Cu-64 dotatate, with the liver being the organ with the highest absorbed radiation dose (0.16 mGy/MBq). The labeled dose of Cu-64 dotatate (4 mCi) results in an effective dose of 4.7mSv.

8.2.6. Safety Analyses by Demographic Subgroups

The Applicant's reported distribution of adverse events in Study RMX-18-22 by age and sex appear below in Table 20 and Table 21, respectively. Meaningful trends are not apparent.

Table 20. Number and Percentage of Subjects With Adverse Events by Age Group in Study RMX-18-22

Parameter	<60 Years N=40 n (%)	60 to 75 Years N=15 n (%)	>75 Years N=8 n (%)	Total N=63 n (%)
Total number of adverse events	6	1	2	9
Subjects with at least one adverse event	3 (7.5)	1 (6.7)	1 (12.5)	5 (7.9)
Gastrointestinal disorders	2 (5.0)		1 (12.5)	3 (4.8)
Nausea	1 (2.5)			1 (1.6)
Vomiting	1 (2.5)		1 (12.5)	2 (3.2)
Nervous system disorders	2 (5.0)			2 (3.2)
Headache	1 (2.5)			1 (1.6)
Syncope	1 (2.5)			1 (1.6)
Skin and subcutaneous tissue disorders	1 (2.5)			1 (1.6)
Melanoderma	1 (2.5)			1 (1.6)
Vascular disorders		1 (6.7)	1 (12.5)	2 (3.2)
Flushing		1 (6.7)		1 (1.6)
Hypertension			1 (12.5)	1 (1.6)

Source: Response to Information Request (SN10, dated 4/9/20)

Table 21. Number and Percentage of Subjects With Adverse Events by Sex in Study RMX-18-22

Parameter	Female N=35 n (%)	Male N=28 n (%)	Total N=63 n (%)
Total Number of Adverse Events	3	6	9
Subjects with at Least One Adverse Event	2 (5.7)	3 (10.7)	5 (7.9)
Gastrointestinal Disorders	1 (2.9)	2 (7.1)	3 (4.8)
Nausea		1 (3.6)	1 (1.6)
Vomiting	1 (2.9)	1 (3.6)	2 (3.2)
Nervous System Disorders	1 (2.9)	1 (3.6)	2 (3.2)
Headache		1 (3.6)	1 (1.6)
Syncope	1 (2.9)		1 (1.6)
Skin and Subcutaneous Tissue Disorders		1 (3.6)	1 (1.6)
Melanoderma		1 (3.6)	1 (1.6)
Vascular Disorders	1 (2.9)	1 (3.6)	2 (3.2)
Flushing		1 (3.6)	1 (1.6)
Hypertension	1 (2.9)		1 (1.6)

Source: Response to Information Request (SN10, dated 4/9/20)

A subgroup analysis of adverse event data by race was also performed for Study RMX-18-22. All reported adverse events occurred in white subjects.

8.2.7. Additional Safety Explorations

Human Reproduction and Pregnancy

There are no data on Cu-64 dotatate use in pregnant women to inform any drug-associated risks. However, all radiopharmaceuticals, including Cu-64 dotatate**,** have the potential to cause fetal harm.

8.2.8. Additional Literature Support of Safety

A published abstract by Kjaer et al., 2019, reported safety experience with Cu-64 dotatate in 500 consecutive patients at a single center in Denmark , including patients described in Pfeifer et al., 2012, Pfeifer et al., 2015, and Johnbeck et al. (Pfeifer et al. 2012; Pfeifer et al. 2015; Johnbeck et al. 2017; Kjaer et al. 2019). The authors reported “no major side-effects” in these 500 patients, although safety monitoring measures were not specified. The review team considered this information as supportive of the Applicant’s submitted safety database.

8.2.9. Integrated Assessment of Safety

The review team identified no major safety issue for Cu-64 dotatate based upon data from trials conducted by the Applicant as well as published literature. Non-serious cases of flushing, nausea, and vomiting were identified as ARs.. From a radiation exposure prospective, the estimated effective dose from Cu-64 dotatate is similar to that of other commonly used diagnostic radiopharmaceuticals, including those used for PET imaging of NET.

8.3. Statistical Evaluation

The NDA submission includes confirmatory evidence for the imaging efficacy and safety of Cu-64 dotatate PET/CT in detecting SSTR-positive NET from a prospective clinical trial, Study RMX-18-22, and a retrospective re-analysis of previously published clinical trial data, the NETMedix Denmark Trial.

Study RMX-18-22

This study was a prospective open-label, single-center, single-dose, single-arm phase 3 clinical trial. A total of 66 subjects including both healthy volunteers and patients with NET were enrolled. Details of the study description can be found in Section 8.1.1. This section covers FDA’s statistical assessments of the study.

The performance of Cu-64 dotatate PET on the co-primary efficacy endpoints for each reader can be found in Table 22. Based on the results, this study is deemed to be a win with the lower bound of the 95% CI for subject-level PPA and NPA exceeding pre-specified thresholds (70% for NPA and 60% for NPA) in all three readers. Note that the Cu-64 dotatate PET of a SOT-negative

subject was interpreted as "unevaluable" by Reader 1, so the denominator of NPA for Reader 1 is 29 while the denominator of NPA for the other two readers is 30.

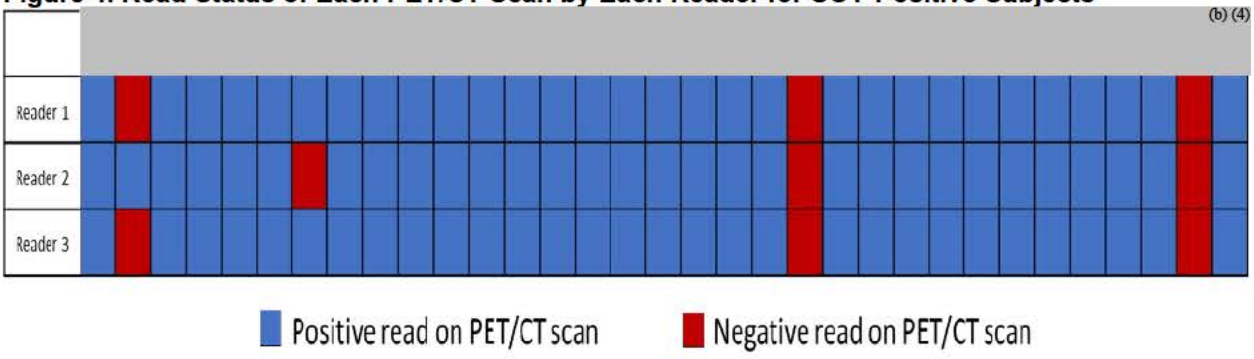
Table 22. Individual Reader Results for Cu-64 Dotatate PET in EE Population (N=63)

	Reference (SOT)	
NET Status as Identified by Reader	**Positive**	**Negative**
Reader 1 (n=62)*		
Positive	30	1
Negative	3	28
Percent reader agreement (95% CI)**	PPA = 0.91 (0.75, 0.98)	NPA = 0.97 (0.80, 0.99)
Reader 2 (n=63)		
Positive	30	6
Negative	3	24
Percent reader agreement (95% CI)**	PPA = 0.91 (0.75, 0.98)	NPA = 0.80 (0.61, 0.92)
Reader 3 (n=63)		
Positive	30	3
Negative	3	27
Percent reader agreement (95% CI)**	PPA = 0.91 (0.75, 0.98)	NPA = 0.90 (0.72, 0.97)

Source: FDA reviewer analysis
* Reader 1 interpreted one of the 63 PET scans as "not evaluable"
** Wilson score interval with continuity correction
Abbreviations: CI. confidence interval; EE, efficacy evaluable; NPA, negative percent agreement; PET, positron emission tomography; PPA, positive percent agreement; SOT, standard of truth

Notable in the study results is that PPA is the same at 0.91 for all the three readers. Figure 4 displays read results of each Cu-64 dotatate PET/CT scan for the 33 SOT-positive subjects by each reader: blue color indicating a positive PET/CT read and red color indicating a negative PET/CT read. The three readers show almost perfect reader agreement: they all incorrectly read PET/CT scans of subjects (b) (6) as negative and only differed in reads for subjects (b) (6) (b) (6) Each reader missed three times in reading the 33 PET/CT scans of SOT-positive subjects, resulting in the same PPA for all three readers.

Figure 4. Read Status of Each PET/CT Scan by Each Reader for SOT-Positive Subjects

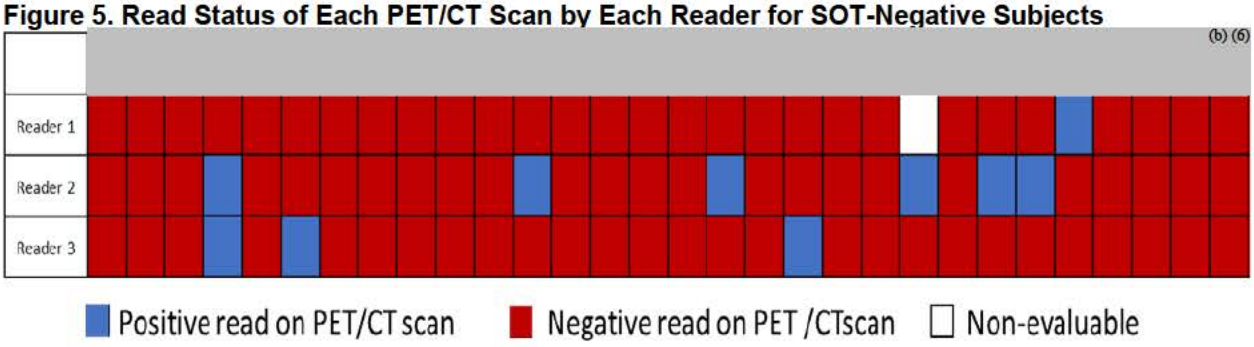


Source: FDA reviewer analysis
Abbreviations: CT, computed tomography; PET, positron emission tomography; SOT, standard of truth

Figure 5 displays read results of each of Cu-64 dotatate PET/CT scan for the 30 SOT-negative subjects by each reader: blue color again indicating a positive PET/CT read, red color indicating a negative PET/CT read, and white color indicating an unevaluable read in a single reader. A lower level of reader agreement compared to that observed in Figure 4 is noted, explaining the

varying degree of NPA among 3 readers. These findings are consistent with the readers interpreting images independently.

Figure 5. Read Status of Each PET/CT Scan by Each Reader for SOT-Negative Subjects



Source: FDA reviewer analysis
Abbreviations: CT, computed tomography; PET, positron emission tomography; SOT, standard of truth

A major statistical concern identified in this confirmatory clinical study is the lack of an objective means of establishing the SOT for NET status. The SOT was determined based on the NET status decision of a single oncologist who reviewed a subject's collective information package including histopathology reports, conventional imaging reports, and all other clinical data such as laboratory tests, signs, and symptoms collected before Cu-64 dotatate PET/CT scanning. No post-PET follow-up of a suspicious lesion on Cu-64 dotatate PET/CT scan, whether by histology/biopsy or by conventional imaging, was performed. This method of SOT determination by a sole oncologist may allow for the introduction of possible bias depending on the oncologist's subjective tendencies on how to combine and collectively interpret various types of clinical information for NET status determination, rendering questionable the accuracy of PPA (sensitivity) and NPA (specificity) results.

An exploratory analysis restricted to patients with histopathology reports available (all of whom were classified as SOT-positive by the oncologist) for PPA evaluation and heathy volunteers (all of whom were classified as SOT-negative by the oncologist) for NPA evaluation was performed. In this exploratory analysis, histopathology reports served as the stand-alone NET status determination. It is noted that these histopathology reports were available at the time of enrollment to confirm that these patients had SSTR-positive NET. Healthy volunteers were confirmed as truly negative for NET through CT review by an independent radiologist in this study. Table 23 presents analysis results on the restricted population.

Table 23. Individual Reader Results for Cu-64 Dotatate PET in Patients With Histopathology Reports Available and Healthy Volunteers (N=41)

NET Status as Identified by Reader	Subjects With Histopathology Report Available N=20	Healthy Volunteers N=21
Reader 1		
Positive	17	1
Negative	3	20
Percent Reader Agreement (95% CI)*	PPA =17/20=0.85 (0.61, 0.96)	NPA =20/21=0.95 (0.74, 0.99)
Reader 2		
Positive	18	3
Negative	2	18
Percent Reader Agreement (95% CI)*	PPA =18/20=0.90 (0.67, 0.98)	NPA =18/21=0.86 (0.63, 0.96)
Reader 3		
Positive	17	2
Negative	3	19
Percent Reader Agreement (95% CI)*	PPA =17/20=0.85 (0.61, 0.96)	NPA =19/21= 0.90 (0.68, 0.98)

Source: FDA reviewer analysis
* Wilson score interval with continuity correction
Abbreviations: CI, confidence interval; NPA, negative percent agreement; PET, positron emission tomography; PPA, positive percent agreement

Overall, Table 23 shows similar PPA and NPA results as those in Table 22. With approximately half the original sample size in the restricted patients available for estimating the PPA (n=41 vs. n=20), the interval estimate of PPA for each reader is expectedly wider, pointing to the larger uncertainty.

NETMedix Denmark Study

The two co-primary efficacy endpoints of the re-analysis of investigator-supplied data in this study were patient-level sensitivity and specificity of Cu-64 dotatate PET/CT in detecting patients with SSTR positive NETs. Alternative statistical hypotheses of sensitivity > 80% and specificity > 60% were evaluated with 95% CIs at the type-1 error rate of 0.025 using Wilson's score method with continuity correction. The results of the re-analysis can be found in Table 15 and Table 16 in Section 8.1.3.

The statistics team identified the same concern as the clinical team regarding the SOT determination of NET status. For example, one of the SOT rules, states that if both Cu-64 dotatate and In-111-pentetreotide were positive, the patient was considered true positive and no further follow-up was needed, and thus includes the use of the investigational Cu-64 dotatate PET imaging for SOT determination. This SOT rule may tend to favor the imaging performance evaluation of Cu-64 dotatate PET. However, the NDA submission includes additional case narratives further illustrating the important roles played by histopathology and follow-up imaging for assessing NET status in certain patients. Careful clinical review of the narratives concluded that final SOT determination was satisfactory overall in these patients (Section 8.1.3). This re-analysis study provides supportive evidence for the imaging performance of Cu-64 dotatate PET determined in Study RMX-18-22.

Statistical Summary:

The results of the prospective phase 3 study RMX-18-22 met success criteria pre-specified in the SPA. A major statistical concern for this confirmatory clinical study is the lack of an objective method of establishing the SOT for NET status. Since there was no follow-up biopsy or longitudinal imaging in patients who had no available histopathology, the NET status in some patients enrolled in study RMX-18-22 relied only on other imaging performed near the time of Cu-64 dotatate PET. Similarly, the NET status determination in the NETMedix Denmark Study was more consistent with a reference standard result rather than a truth standard result. Therefore, defining imaging performance of Cu-64 dotatate with PPA and NPA is more appropriate than defining its imaging performance with sensitivity and specificity. The results of PPA and NPA obtained in the NETMedix Denmark Study provide supportive evidence for the imaging performance of Cu-64 dotatate PET as determined in Study RMX-18-22.

8.4. Conclusions and Recommendations

The reviewed data adequately support the efficacy of Cu-64 dotatate PET for imaging of NET in adults. No safety signal was identified in the data. The review team finds the benefit-risk balance of Cu-64 dotatate to be favorable and recommends approval.

The primary efficacy analyses in Study RMX-18-22 and the NETMedix Denmark Study directly support a claim of patient-level detection of NET by Cu-64 dotatate PET. However, additional lesion-level and region-level results in these and other reviewed trials suggest that extrapolation of efficacy to a localization claim may be reasonable, although related primary data were predominantly unavailable. Both Ga-68 dotatate and Ga-68 dotatoc are approved for localization of NET. The shared mechanism of action and molecular target of these PET drugs and Cu-64 dotatate further support maintaining class-wide consistency in labeled indications. Of note, NET detection can be considered to be inherent in a localization claim.

(b) (4)

9. Advisory Committee Meeting and Other External Consultations

No advisory committee meeting or external consultation was needed for this NDA.

10. Pediatrics

This application did not contain any pediatric data. On May 18, 2018, Cu-64 dotatate was granted orphan drug designation as a diagnostic for the management of neuroendocrine tumors. Therefore, this application is exempt from the PREA requirements.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Section 1: Indications and Usage

- As discussed in Section 8.4 of this review, the Applicant's proposed (b) (4) localization (b) (4) claims were revised to a localization claim.

Section 2: Dosage and Administration

- Consistent with the labeling of other PET drugs, the following language was added to section 2.1: Radiation Safety-Drug Handling. Use of the word "minimize" was deemed appropriate given the context and precedent in the labeling of other PET drugs.

Handle copper Cu64 dotatate (Cu 64 dotatate) injection with appropriate safety measures to minimize radiation exposure.

- As discussed in Section 6 of this review, the imaging acquisition start time was recommended to be 45 to 90 minutes after injection.

Section 5: Warnings and Precautions

- Consistent with other PET drugs in this class, the language below was placed in section 5.2: Risk for Image Misinterpretation. Given the context, other information in the label, and precedent in the labeling of this class of PET drugs, it was not deemed necessary to qualify this language with a statement that efficacy for detecting tumors other than NET has not been established.

The uptake of Cu 64 dotatate 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. uncinate process of the pancreas).

- As discussed in Section 8.1.5 of this review, the following language was also added in section 5.2: Risk for Image Misinterpretation:

A negative scan after the administration of [trade name] in patients who do not have a history of NET disease does not rule out disease.

Section 6: Adverse Reactions

- As discussed in Section 8.2 of this review, ARs of flushing, nausea, and vomiting were listed as occurring in less than 2% of the subjects in Study RMX-18-22 and Study RMX-17-22.
- As also discussed in Section 8.2 of this review, transient nausea was listed as an AR in 4 out of the 126 patients with available safety results in the submitted published literature.

Section 7: Drug Interactions

- The following similar language as that which appears in labeling for other PET drugs in this class was placed in section 7.1: Somatostatin Analogs:

Non-radioactive somatostatin analogs and Cu 64 dotatate competitively bind to somatostatin receptors (SSTR2). Image patients just prior to dosing with somatostatin analogs. For patients on long-acting somatostatin analogs, a wash-out period of 28 days is recommended prior to imaging. For patients on short-acting somatostatin analogs, a washout period of 2 days is recommended prior to imaging.

Section 8: Use in Specific Populations

- In section 8.2 Lactation, the Applicant's originally proposed recommendation to interrupt breastfeeding for (b) (4) hours was revised to 12 hours based upon FDA modeling that considered total newborn effective dose from estimated radiation exposure. Use of the phrase, "to minimize radiation exposure", was deemed appropriate given the context and precedent in the labeling of other PET drugs.

- Given the orphan drug related exemption from PREA and lack of submitted pediatric data, the following language was added to section 8.4: Pediatric Use:

The safety and effectiveness of [trade name] have not been established in pediatric patients.

Section 12: Clinical Pharmacology

- As discussed in Section 15.3 (OCP appendices) of this review, (b) (4) were removed (b) (4)

Section 14: Clinical Studies

- Study RMX-18-22 was described in detail, including per-reader PPA and NPA results.
- Given its supportive role, the NETMedix Denmark Study was briefly mentioned as demonstrating similar imaging performance as that of Study RMX-18-22.

12. Risk Evaluation and Mitigation Strategies

A risk evaluation and mitigation strategy is not needed for this product.

13. Postmarketing Requirements and Commitments

There are no postmarketing requirements or commitments for this application.

14. Office Director (or Designated Signatory Authority) Comments

I have reviewed the information in this document and concur with the conclusions and recommendations of the review staff.

15. Appendices

15.1. References

Graham, MM, X Gu, T Ginader, P Breheny, and JJ Sunderland, 2017, (68)Ga-DOTATOC imaging of neuroendocrine tumors: A systematic review and metaanalysis, J Nucl Med, 58(9):1452-1458.

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Kjaer, A, T Binderup, C Johnbeck, E Carlsen, S Langer, B Federspiel, and U Knigge, 2019, 64Cu-DOTATATE somatostatin receptor imaging in neuroendocrine tumors: experience from 500 patients at Copenhagen ENETS Center of Excellence, J Nucl Med, 60.

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Pfeifer, A, U Knigge, J Mortensen, P Oturai, AK Berthelsen, A Loft, T Binderup, P Rasmussen, D Elema, TL Klausen, S Holm, E von Benzon, L Hojgaard, and A Kjaer, 2012, Clinical PET of neuroendocrine tumors using 64Cu-DOTATATE: First-in-humans study, J Nucl Med, 53(8):1207-1215.

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(Tyr(3))octreotate and AN-238 in a mouse pheochromocytoma model, Theranostics, 6(5):650-665.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): RMX-17-22, RMX-18-22, NETMedix Denmark

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.3.1. Summary of Bioanalytical Method Validation and Performance

Were relevant (b) (4) measured in the clinical pharmacology and biopharmaceutics studies?

No. (b) (4) (see below for more details).

(b) (4)

Overall the precision, accuracy, selectivity, and performance of the assays were not acceptable and did not meet FDA recommended criteria. The PK data in plasma was omitted in labeling. Total radioactivity in urine over 6-hours collection was reported in labeling.

15.4. Additional Clinical Outcome Assessment Analyses

None.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Ronald Honchel, Ph.D.	OSM/DIRM	Sections: 5	**Select one:** X Authored ___ Approved
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Nonclinical Team Leader	Adebayo Laniyonu, Ph.D.	OSM/DIRM	Sections: 5	**Select one:** ___ Authored X Approved
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Clinical Pharmacology Reviewer	Edwin C. Y. Chow, Ph.D.	OCP/DCPII	Sections: 6 and 15.3	**Select one:** X Authored ___ Approved
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Clinical Pharmacology Team Leader	Christy John, Ph.D.	OCP/DCPII	Sections:6 and 15.3	**Select one:** ___ Authored X Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Division Director	Brian Booth Ph.D.	OCP/DCPI	Sections: 6 and 15.3	**Select one:** ___ Authored X Approved
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Clinical Reviewer	Brenda Ye, M.D.	OSM/DIRM	Sections: All	**Select one:** X Authored ___ Approved
	Signature:			
Clinical Team Leader/Cross-Disciplinary Team Leader (CDTL)	August Hofling, M.D., Ph.D.	OSM/DIRM	Sections: All	**Select one:** X Authored X Approved
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	Signature: Sungwon Lee			
Statistical Secondary Reviewer	Jyoti Zalkikar, Ph.D.	OB/DBI	Section: 8	**Select one:** X Authored ___Approved
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Statistical Tertiary Reviewer r and Acting Deputy Division Director (DBI)	Sue Jane Wang, Ph.D.	OB/DBI	Sections: 8	**Select one:** ___ Authored X Approved
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Office Director (OSM)	Charles Ganley, M.D.	OSM	Sections: All	**Select one:** ___ Authored _X_ Approved
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