1 TITLE PAGE

STUDY TITLE:	An Open-label, Single-dose, Single-arm, Single-center Clinical Trial of ^{64}Cu-DOTATATE (NETMedix™) PET-CT Scan for Imaging Patients with Known or Suspected Somatostatin Receptor-positive Neuroendocrine Tumors (NETs)
PROTOCOL NUMBER:	RMX-18-22
NCT number	NCT03673943
STUDY PHASE:	Phase 3
IVESTIGATIONAL PRODUCT:	NETMedix™ (^{64}Cu-DOTATATE) injection, for intravenous use
DRUG SUBSTANCE	^{64}Cu-DOTATATE
STUDY DATES:	January 22, 2018 to December 2, 2018
INDICATION:	Imaging of patients with known or suspected somatostatin receptor-positive neuroendocrine tumors
SPONSOR CONTACT INFORMATION:	Ebrahim S. Delpassand, MD, FACNM RadioMedix, Inc. 9701 Richmond Avenue, Suite 222 Houston, TX 77042 +1 (713) 358-6570
REPORT DATE:	March 6, 2019
LEAD INVESTIGATOR:	Rodolfo Nunez, M.D.
GCP COMPLIANCE:	The investigators agreed to conduct the study in compliance with the study protocol, the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use guidance for industry entitled "E6 Good Clinical Practice (GCP): Consolidated Guidance", the "Declaration of Helsinki: Ethical Principles for Research Involving Human Subjects" (World Medical Association), and applicable law and regulatory requirements.

2 SYNOPSIS

NAME OF SPONSOR/COMPANY: RadioMedix, Inc. NAME OF TEST PRODUCT: NETMedix™ (^{64}Cu-DOTATATE) injection, for intravenous use NAME OF ACTIVE INGREDIENT: ^{64}Cu-DOTATATE	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Title of Study: An Open-label, Single-dose, Single-arm, Single-center Clinical Trial of ^{64}Cu-DOTATATE (NETMedix™) PET-CT Scan for Imaging Patients with Known or Suspected Somatostatin Receptor-positive Neuroendocrine Tumors (NETs)

Principal Investigator: Rodolfo Nunez, M.D.

Publication (ref.):

Study Period:	**Phase of Development:**
Date First Subject Enrolled: January 22, 2018 Date Last Subject Completed: December 2, 2018	Phase 3

Objectives:

Primary Objective:

- To assess the performance (sensitivity and specificity) of ^{64}Cu-DOTATATE PET-CT imaging in subjects with known or suspected NETs, when comparing individual reader results to a standard of truth (SOT) for each subject.

Secondary Objectives:

- To characterize the predictive value of ^{64}Cu-DOTATATE PET-CT imaging when comparing an imaging reader-majority rule determination to the SOT for each subject and also when the comparison was performed on an individual reader basis.
- To evaluate the imaging performance (sensitivity and specificity) of ^{64}Cu-DOTATATE when comparing an imaging reader-majority rule determination to the SOT for each subject.
- To evaluate the imaging performance of ^{64}Cu-DOTATATE to determine if subjects had metastatic or localized disease as compared to the SOT.

Tertiary Objective:

- To evaluate the intra-reader reliability and inter-reader agreement.

Exploratory Objective:

- To evaluate pharmacokinetics and identify any major ^{64}Cu moieties other than intact parent drug (^{64}Cu-DOTATATE), free ^{64}Cu and known radiolysis byproducts of parent drug.

NAME OF SPONSOR/COMPANY: RadioMedix, Inc. NAME OF TEST PRODUCT: NETMedix™ (^{64}Cu-DOTATATE) injection, for intravenous use NAME OF ACTIVE INGREDIENT: ^{64}Cu-DOTATATE	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Methodology:

This was an open-label, single-dose, single-arm, single-center imaging study using DOTATATE peptide, labelled with the ^{64}Cu tracer. In total, 59 subjects were expected to be recruited in the study. The study recruited both healthy volunteers as well as patients with confirmed or suspicion of NET disease by histology or conventional anatomical and functional imaging modalities including but not limited to magnetic resonance imaging (MRI), and/or computed tomography (CT), and/or, F-18 FDG PET/CT and /or F-18 NaF bone PET/CT and/or bone scintigraphy, and/or Octreoscan®.

For safety assessment, vital signs were measured within 30 minutes before and up to 1 hour after administration of ^{64}Cu-DOTATATE. A blood sample was collected within 30 minutes before the injection and within 2 hours post ^{64}Cu-DOTATATE administration to assess clinical chemistries and haematology.

Any adverse events observed or reported were recorded for up to 48 hours following study drug administration. In addition, observed or patient reported immediate adverse events including but not limited to pain, injection site reaction, headache, nausea, vomiting, flushing or other as reported, were assessed within 1 hour before and within 2 hours after the study drug administration.

All subjects underwent a continuous ECG recording at least 15 minutes prior to administration of the study drug 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 study drug administration. All the ECG data were collected in digital format, analysed and reviewed (with manual over-read) by an independent physician to determine normal or abnormal and if abnormal, whether clinically significant or not significant.

To assess pharmacokinetics, blood and urine samples were collected after the administration of ^{64}Cu-DOTATATE on 6 subjects. Five 10 mL blood samples were collected at 1, 10, 30, 60, and 120 minutes after the administration of ^{64}Cu-DOTATATE. Urine samples were collected in three intervals after the administration of ^{64}Cu-DOTATATE; 0-60 minutes, 60-120 minutes, and 120-360 minutes. The pharmacokinetic (PK) analysis was focused only on radiometric detection using a bioanalytical high performance liquid chromatography (HPLC) method.

Number of Subjects (planned and analyzed):

Planned: It was anticipated that a total of 59 subjects would be recruited. The study population comprised of both healthy volunteers and patients with lesions confirmed or suspicious for NETs. The efficacy analysis sample size was planned to be 63 evaluable subjects, 59 subjects from this phase 3 study and 4 subjects from the selected 4.0 mCi dose cohort of the phase 1 study. This sample size was appropriate to achieve statistical power for the primary endpoints of this clinical trial. It was anticipated that the PK assessment would be performed on 6 subjects.

Analyzed: The study enrolled 66 subjects including 4 subjects from the Phase 1 study. In total, 63 subjects (59 from the Phase 3 study and 4 from the Phase 1 study) were injected with study drug at an intended dose of 4.0 mCi and met the criteria to be analyzed for safety and efficacy.

Diagnosis and Main Criteria for Eligibility:

Inclusion Criteria:

Patients

1. Subjects of either sex, aged ≥18 years.
2. Met at least one of the following criteria:
    a. Confirmed or suspicion of NET based on histology/ biopsy report.
    b. Confirmed or suspicion of NET based on conventional imaging scans of affected area such as MRI and/or contrast enhanced CT and/or an FDG PET-CT scan and/or NaF PET-CT scan and/or OctreoScan® performed within 8 weeks prior to study date.

Healthy volunteers

Healthy male or female subjects age ≥18 years of age and in good health as determined by absence of clinically relevant abnormalities determined by a full medical history, physical examination, vital signs and clinical laboratory tests.

Patients and Healthy volunteers

1. Willing to sign informed consent form.
2. Able to understand and comply with the procedures and requirements of the study.
3. Negative pregnancy test in women of child-bearing potential, performed on the day of the study, using urine or blood-based testing.
4. For women of childbearing potential, agreement to remain abstinent (refrain from heterosexual intercourse) or use non-hormonal contraceptive methods for at least 2 weeks following administration of study drug.
5. For men, agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures for at least 2 weeks following administration of study drug;
6. Recent blood test results (within 4 weeks pre-dose) as follows:
    a. WBC: $>2\times10^9$/L
    b. Haemoglobin: >8.0g/dL
    c. Platelets: $>50\times10^9$/L
    d. ALT, AST, AP: ≤5 times ULN
    e. Bilirubin: ≤3 times ULN
    f. Serum creatinine: <170 μmol/L

Exclusion Criteria:

Subjects must not have had any of the following conditions to be enrolled in this study:

1. Pregnant or planning to become pregnant within the next two weeks.
2. Inability to provide written consent.
3. Therapeutic use of any somatostatin analogue, including Sandostatin® LAR (within 28 days) and Sandostatin® (within 2 days) prior to study imaging. If a subject is on Sandostatin® LAR, a wash-out period of 28 days was required before the injection of the study drug.
4. History or presence of significant hematological abnormalities or immunodeficiency or any condition that might compromise the immune system (infection, vaccination), or any etiology as indicated by clinically significant abnormal values of any of the following hematologic parameters: platelets, hemoglobin, WBC count and ANC.
5. Lactating and breast-feeding women.
6. Acute or chronic clinically significant conditions such as uncontrolled congestive heart failure, liver or kidney dysfunction, uncontrolled hypertension
7. History of hypersensitivity to drugs with a similar chemical structure to the investigational product or any of its excipients
8. History of significant drug abuse within 1 year prior to screening or use of soft drugs (such as marijuana) within 3 months prior to the screening visit or hard drugs (such as cocaine, phencyclidine, and crack) within 1 year prior to screening

9. Participation in other clinical research trials involving evaluation of other investigational treatments within 30 days prior to enrollment and/or unwilling to allow at least one week before participation in another drug trial following the current study.

Test Product, Dose and Mode of Administration:

The drug product NETMedix™ Injection Solution contained ^{64}Cu-DOTATATE filled in a glass vial, closed with butyl rubber stopper secured with an aluminum crimp seal. The drug product was delivered by RadioMedix Inc. to the clinical site. The study drug was administered as an intravenous bolus injection.

Duration of Treatment:

The duration of subject participation was from the time of signing the informed consent form through the 2-day post-injection visit. A subject was deemed enrolled in the study once the subject signed the informed consent form.

Reference Therapy, Dose and Mode of Administration:

This was a single-dose, single-arm study. There was no reference therapy. The study drug was administered as an intravenous bolus injection. The injection was given by hand into a 22 or 24-gauge catheter at a rate of 3-4 mL/min. The catheter was flushed with 3 mL of normal saline post-injection. The radioactivity/dose was measured before and after injection using a calibrated machine and recorded. The difference in radioactivity before the injection and after injection was considered as the total injected dose.

CRITERIA FOR EVALUATION:

Efficacy Endpoints:

The co-primary effectiveness endpoints were the sensitivity and specificity of ^{64}Cu-DOTATATE PET-CT imaging when each imaging reader's subject-level result was compared to a SOT for the subject, with primary endpoint success defined as the same two out of three readers having sensitivity and specificity results exceeding the specified thresholds.

The secondary effectiveness endpoints of the study were:

- Majority of readers sensitivity;
- Majority of readers specificity;
- Majority of readers positive predictive value (PPV);
- Majority of readers negative predictive value (NPV);
- Majority of readers accuracy;
- Individual reader sensitivity and specificity in distinguishing between localized and metastatic disease;
- Majority reader sensitivity and specificity in distinguishing between localized and metastatic disease;
- Individual reader accuracy, PPV, and NPV.

The tertiary effectiveness endpoints of the study were:

- Intra-reader agreement using Cohen's Kappa
- Inter-reader agreement using Cohen's Kappa

Safety Assessments:

Safety was evaluated by review of the following:

- Adverse events
- Changes in vital signs

- Changes in clinical laboratory parameters
- Changes in ECG recordings

Pharmacokinetic Assessments:
PK analysis was performed as recommended by FDA using a bioanalytical HPLC method focused only on radiometric detection that could separate intact parent drug (^{64}Cu-DOTATATE), free ^{64}Cu, and known radiolysis byproducts of ^{64}Cu-DOTATATE.

- Identifying any major ^{64}Cu moieties other than intact parent drug (^{64}Cu-DOTATATE), free ^{64}Cu, and known radiolysis byproducts of ^{64}Cu-DOTATATE in plasma and urine samples.

RESULTS:

Treatment and Disposition:

A total of 68 subjects were screened for this study. Of these, 66 were enrolled and 63 (95.5%) completed the study. Three subjects (4.5%) withdrew consent. A total of 63 subjects were injected with a mean dose of 4.11 mCi of ^{64}Cu-DOTATATE.

Efficacy Results:

- Based on the individual reader analysis, all three readers demonstrated success on the co-primary effectiveness endpoints with Sensitivity >70% and Specificity >60%.
- The majority read analysis showed statistically significant sensitivity (0.9091, p=0.0042) and specificity (0.9655, p<0.0001) in detecting patients positive for disease and patients negative for disease, respectively. The probability of disease being present given a positive result with ^{64}Cu-DOTATATE (PPV) was 0.9677. The probability of disease being absent given a negative result with ^{64}Cu-DOTATATE (NPV) was 0.9032. In this study, the majority read analysis determined that imaging with ^{64}Cu-DOTATATE had an accuracy of 0.9355.
- The majority read analysis had a sensitivity of 1.000 and a specificity of 1.000 in distinguishing localized or metastatic disease among patients imaged with ^{64}Cu-DOTATATE and having an image status of positive for disease.
- All readers demonstrated a level of accuracy ranging from 0.8571 to 0.9355. Readers 1 and 3 were more accurate in determining the presence or absence of disease relative to the SOT than Reader 2. Reader 1 had a PPV of 0.9677, NPV of 0.9032, and accuracy of 0.9355; Reader 2 had a PPV of 0.8333, NPV of 0.8889, and accuracy of 0.8571; and Reader 3 had a PPV of 0.9091, NPV of 0.9000, and accuracy of 0.9048.
- Overall, the 3 readers demonstrated a high degree of inter-reader agreement (Kappa = 0.7664).
- Relative to the 7 images that were re-read, Readers 1 and 3 demonstrated perfect intra-reader reliability upon image re-read (Kappa = 1.000).
- It can be concluded that ^{64}Cu-DOTATATE is an effective imaging agent in detecting the presence or absence of a NET.

Safety Results:

- Overall there were 9 adverse events experienced by 5 subjects. The most common adverse events by MedDRA system organ class were gastrointestinal disorders (4.8%), nervous system disorders (3.2%), vascular disorders (3.2%), and skin and subcutaneous disorders (1.6%).
- All adverse events were either mild or moderate in severity. There were no adverse events that were severe, life-threatening or disabling, or that resulted in death. Adverse events that were mild in severity included nausea, vomiting, headache, melanoderma, and flushing. Adverse events that were moderate in severity included syncope and hypertension.
- All adverse events were either probably not related or definitely not related to injection of a single dose of ^{64}Cu-DOTATATE. No adverse events were considered definitely related, probably related, or possibly related to ^{64}Cu-DOTATATE injection.
- There were no serious adverse events reported in subjects injected with ^{64}Cu-DOTATATE.
- There were no clinically significant changes from baseline in mean serum chemistry or hematology values that occurred post-injection with ^{64}Cu-DOTATATE or at the Day 1-2 follow-up visit.
- There were no clinically significant changes from baseline in mean vital signs occurring at 5-, 10-, 30-, or 60- minutes post-injection or at discharge.
- There were no shifts observed in ECG parameters from baseline to 1 hour post-injection of ^{64}Cu-DOTATATE.
- Injection of a single dose of ^{64}Cu-DOTATATE appears to be safe and well tolerated in this patient population.

CONCLUSIONS:

On the basis of these findings, the following overall conclusions can be drawn:

- ^{64}Cu-DOTATATE has both a high sensitivity and specificity in detecting patients with and without NETs, respectively.
- ^{64}Cu-DOTATATE has a high sensitivity and specificity in determining localized or metastatic disease.
- ^{64}Cu-DOTATATE PET-CT image reads have a high level of inter-reader and intra-reader agreement.
- Imaging with ^{64}Cu-DOTATATE appears to be safe, effective, and well tolerated.

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4 ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AP	alkaline phosphatase
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CI	confidence interval
CMC	chemistry manufacturing and control
(i)CRF	(internet)case report form
CRO	contract research organization
CT	computed tomography
Cu	copper
ECG	electrocardiogram
EE	efficacy evaluable
FDA	United States Food and Drug Administration
FDG	fluorodeoxyglucose
FN	false negative
FP	false positive
GCP	Good Clinical Practice
GH	growth hormone
GI	gastrointestinal
HPLC	high performance liquid chromatography
hrs	hours
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IGF	insulin-like growth factor
IND	Investigational New Drug
IRB	Institutional Review Board
L	liter
mCi	millicurie
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
MeV	mega electron volt
µg	microgram
min	minute
mL	milliliter
mm	millimeter
MRI	magnetic resonance imaging
NET	neuroendocrine tumor
NPV	negative predictive value
ns	nanosecond
PI	Principal Investigator
PK	pharmacokinetic
PPV	positive predictive value
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SE	standard error
SOC	system organ class
SOT	standard of truth
SPECT	single photon emission computed tomography
SRIF	somatotropin release inhibiting factor
SRS	somatostatin receptor scintigraphy
SST	somatostatin
SSTR	somatostatin receptor
TEAE	Treatment Emergent Adverse Event
TN	true negative
TP	true positive
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VIP	vasoactive intestinal peptide
v/v	volume/volume
WBC	white blood cell
WHO	World Health Organization
w/v	weight/volume

5 ETHICS

5.1 INSTITUTIONAL REVIEW BOARD

A properly constituted, valid Institutional Review Board (IRB) reviewed and approved the protocol, the investigator's permission/informed consent form (ICF) documents, and related subject information and recruitment materials before the start of the study.

It was the responsibility of the Investigator to obtain written informed consent from each individual participating in the study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The Investigator also explained to the subjects that they were free to refuse to enter the study or to withdraw from it at any time. All ICF documentation contained all the elements described in 21 CFR Part 50.

Protocol amendments were reviewed and approved by the IRB. Written approval from the IRB or a designee was provided to RadioMedix before implementation. This written approval consisted of a completed IRB approval form or written documentation from the IRB containing the same information.

The name of the IRB that approved the conduct of this study and a sample ICF are provided in the appendices.

5.2 ETHICAL CONDUCT OF THE STUDY

The study was conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996) and all applicable regulations, including the US Code of Federal Regulations dealing with clinical studies, and all national and local laws and regulations. Compliance with these regulations and guidelines also constituted compliance with the ethical principles described in the current revision of the Declaration of Helsinki (as modified by the 48th General Assembly, Somerset West, Republic of South Africa, October 1996. This study was carried out in accordance with local legal requirements.

5.3 SUBJECT INFORMATION AND CONSENT

Subjects were required to be registered with the site for verification of eligibility and the assignment of a study identification. The study site personnel registering the subject completed the appropriate baseline information, eligibility checklist, and required registration. Once eligibility was confirmed, the study site personnel conducted the consent discussion with the subject and once consent was obtained (signature of informed consent form as described in the next paragraph), the subject was considered enrolled in the study. The completed source documentation obtained for eligibility verification and registration was kept in the subject's medical records for monitoring purposes.

A signed informed consent form (ICF) was obtained from each research participant (referred to as 'subject') or the subject's legally acceptable representative(s) prior to the subject's participation in the trial. The investigator or qualified designee was responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific procedures were performed (i.e., all procedures not considered standard of care).

The acquisition of informed consent was documented in the subject's medical records and the ICF was signed and personally dated by the subject or the subject's legally acceptable representative(s) and by the person who conducted the informed consent discussion (not necessarily an investigator). The original signed ICF was retained in accordance with institutional policy, and a copy of the signed consent form was provided to the subject prior to participation in the trial.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 INVESTIGATORS

This was a single-center study. A list of investigators and study center location is provided below and in Appendix 16.1.4.

6.2 ADMINISTRATIVE STRUCTURE

The following is a list of individuals and organizations critical to the conduct of the study:

STUDY SITE CENTER	Excel Diagnostics and Nuclear Oncology Center 9701 Richmond Ave. Houston, TX 77042 The list of investigators is in Appendix 16.1.4.
CLINICAL TRIAL MANAGER	David Ranganathan, PhD RadioMedix
CLINICAL MONITOR	Simon Blackburn STATKING Clinical Services
MEDICAL MONITOR	Ebrahim S. Delpassand, MD, FACNM RadioMedix
BIOSTATISTICIAN	Dennis Clason, PhD STATKING Clinical Services
CLINCAL STUDY REPORT AUTHOR	Lindsay Cordes, PharmD STATKING Clinical Services

7 INTRODUCTION

7.1 BACKGROUND

Neuroendocrine tumors (NETs) are a heterogeneous group of rare neoplasms that originate from neuroendocrine cells. These neoplasms occur mostly in the gastrointestinal tract and pancreas (so called gastro-entero-pancreatic NET), but can also occur in other tissues including thymus, lung, and other uncommon sites such as ovaries, heart and prostate. Regardless of their primary site, NETs share histological, immunohistochemical and ultrastructural features (Raut, 2006). NETs retain multi-potent differentiation capacities including the ability to produce and secrete a variety of metabolically active substances including amines, peptides and prostaglandins. Symptoms of NETs are usually vague, nonspecific and vary by the affected organ (Horton, 2004). Thus; non-functional NETs are not associated with any specific hormonal syndrome, instead, their clinical manifestations are similar to most solid tumors, i.e. causing mass-effect either inside the organ where the tumor is growing or pressuring adjacent organs and structures. Regardless of their functional capability, most differentiated NETs express somatostatin receptors on their cell surface.

The endocrine-related characteristics of NETs arise from the enterochromaffin and enterochromaffin-like cells of the gut. Pancreatic, enteric and unknown origins account for most NETs (>85%). Glucagonomas, VIPomas, and somatostinomas (pancreatic) are the rarest (Fauci, 1998; Robertson, 2006), the combined incidence accounting for only 2% of these neoplasms.

^{64}Cu-DOTATATE (the test product) is a radiolabeled receptor-targeted diagnostic product for the detection of somatostatin receptor expressing NETs. The product consists of a somatostatin receptor-targeting peptide complex that is radiolabeled with the isotope ^{64}Copper which has a physical half-life of 12.7 hours.

The use of somatostatin analogues for the diagnosis of neuroendocrine tumors was first established by ^{111}In-pentetreotide (OctreoScan™, available since 1995) (Krenning, 1996). Since then, OctreoScan™ has provided good specificity in whole body SRS-SPECT. Somatostatin receptor (SSTR) has 5 subtypes. However, ^{111}In-pentetreotide has no affinity for SSTR1 and SSTR4, low affinity to SSTR3 and SSTR5, and only high affinity to SSTR2 (Gorges, 2001). Thus, the primary tumor is not identified in 20-50% of NETs. There are three reasons for the relatively high detection failure. Firstly, gamma camera imaging sensitivity is lower than PET, so visualization of deep lesions can be impaired. Secondly, most somatostatin receptor-positive tumors express multiple SSTR subtypes simultaneously. Thirdly, even in the same subject the SSTR expression is heterogeneous.

7.2 CHARACTERISTICS OF ^{64}Cu-DOTATATE

The somatostatin analog octreotate is similar to octreotide except the C-terminal threoninol is replaced with threonine. Octreotate has been conjugated to DOTA forming DOTA-Octreotate (DOTATATE). DOTATATE shows improved binding to SSTR-positive tumors in animal models (de Jong, 1998). Reubi et al. reported a 9-fold increase in the affinity for SST 2, the receptor with the highest expression in most NETs, for DOTATATE as compared to DOTATOC (Reubi, 2000). This finding has been confirmed in clinical studies, which demonstrated that while uptake in the kidneys, liver and spleen were comparable for DOTATOC and DOTATATE, tumor uptake of DOTATATE was 3 to 4 fold higher (Kwekkeboom, 2003). Therefore, ^{64}Cu-DOTATATE PET-CT potentially represents an improvement over the diagnostic agent Octreoscan because of the higher absorbed doses that can be achieved for most tumors. Encouraging clinical results have been reported for ^{64}Cu-DOTATATE PET-CT (Pfeifer, 2012; Pfeifer, 2015).

^{64}Cu-DOTATATE has 3 main components, namely the somatostatin analogue Octreotate, the chemical linker DOTA (tetraxetan) and the positron emitter ^{64}Copper. These three components have been previously used in human subjects and in medical research.

DOTA is a well-established bifunctional chelating agent first used in the 1970s (Stetter, 1976), with chemical formula 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, a 12 member tetraaza macrocycle, essentially a cyclen skeleton that has been modified with acetate side arms to form a polyamino carboxylic acid. At the time of its discovery DOTA was demonstrated to have the largest known formation constant for the complexation Ca^{2+} and Gd^{3+} ions. A modified version of DOTA C-functionalized to act as a bifunctional chelating agent was first reported in 1988. DOTA is the most frequently used moiety for elemental labeling, typically metal isotopes to proteins (antibodies and peptides). There are several derivatives of DOTA also used in investigational medicine, such as DOTATOC ((DOTA (0)-Phe (1)-Tyr (3)) octreotide) or edotreotide) and DOTATATE ((DOTA (0), Phe1, Tyr3)-octreotate). A gallium 68 radiolabeled DOTATATE imaging agent (NETSPOT) and a lutetium 177 radiolabeled DOTATATE analog (LUTETHERA) have been approved by the FDA for localization and treatment, respectively, of NETs in adult and pediatric patients.

Copper (Cu) is a metallic element. Copper has two stable isotopes, ^{63}Cu and ^{65}Cu, along with 27 radioisotopes. The most stable of these is ^{67}Cu with a half-life of 61.83 hours. The least stable is ^{54}Cu with a half-life of approximately 75 ns. Most have half-lives under a minute. Unstable copper isotopes with atomic masses below 63 tend to undergo β+ decay, while isotopes with atomic masses above 65 tend to undergo β− decay. ^{64}Cu decays by both β+ and β−. ^{64}Cu (17% β+; maximum positron energy, 0.653 MeV; half-life [$t_{1/2}$], 12.7 h) is a positron emitter making it a viable PET imaging radionuclide which can give real time images of the physiological processes in the system. ^{64}Cu has been previously used in investigational pharmaceutical preparations such as ^{64}Cu-ATSM, ^{64}Cu-DOTATATE and ^{64}Cu-TETATATE (Lewis, 1999). ^{64}Cu-ATSM [diacetyl-bis (N4-methylthiosemicarbazone)] is being studied as a possible cancer therapy (Lewis, 2001), ^{64}Cu-ATSM is preferentially taken up by hypoxic cells compared to normoxic cells; the extent of retention in tissue is inversely related to the state of tissue oxygenation allowing the quantitation of tissue hypoxia PET imaging. In addition, the radioactive copper moiety of this agent may deliver a selective cytotoxic dose of beta radiation to hypoxic tumor cells. ^{64}Cu-DOTATATE or DOTATOC and ^{64}Cu-TETATATE, are somatostatin analogues that have been researched for the diagnosis of neuroendocrine tumours.

The natural peptide hormones somatostatin-14 and somatostatin-28 (also known as Somatotropin Release Inhibiting Factor; (SRIF) are widely expressed in the central nervous system, hypothalamus, gastrointestinal (GI) tract and the D-cells of the pancreas. On target tissues such as brain, pituitary, pancreas and the GI tract, SRIF peptides bind with high affinity to membrane receptors and through this binding exert a number of biological effects (Hoyer, 1994). Somatostatins are important inhibitory regulators of endocrine and exocrine secretion that reduce the release of a large number of hormones such as growth hormone (GH), glucagon, insulin, gastrin, secretin and thyroid-stimulating hormone (TSH). Furthermore, SRIF peptides in the brain were shown to act as neurotransmitters / neuromodulators that affect locomotor activity as well as cognitive and behavioral processes (Hoyer, 1994).

The neuroendocrine activity of SRIF is well documented by its effective inhibition of GH release. GH is released from the pituitary gland in a pulsatile manner, which leads to IGF-1 synthesis in the liver as well as in other peripheral organs such as heart and kidney. Furthermore, a GH-independent regulation of IGF-1 plasma levels by somatostatin has been documented previously (Serri, 1992).

In the pancreas somatostatin suppresses the release of glucagon from α cells as well as insulin release from pancreatic β cells, thus affecting glucose metabolism. Octreotide has been reported previously to be more selective than insulin in reducing glucagon secretion (Karashima, 1987). As noted above, the NET-selectivity of octreotide and octreotate is based upon their function as analogues of somatostatin.

7.3 BACKGROUND OF CLINICAL DEVELOPMENT

^{64}Cu-DOTATATE is a radiolabeled receptor-targeted imaging product for the detection and monitoring of somatostatin receptor expressing NETs by Positron Emission Tomography (PET) imaging. The product consists of a somatostatin receptor-targeting peptide complex that is radiolabeled with the isotope, ^{64}Copper (^{64}Cu), which has a physical half-life of 12.7 hours.

^{64}Cu-DOTATATE offers several advantages over a recently approved imaging agent for neuroendocrine tumors (NETs), NETSPOT™ and overcomes shortcomings of Ga-68 based NET imaging agents.

a. ^{64}Cu is a cyclotron produced positron emitter.
b. Longer half-life of ^{64}Cu allows centralized production and unit dose dispensing and flexible patient scheduling.
c. Robust, scaled up, well-controlled and centralized manufacturing of $^{64}CuCl_2$ is possible.
d. No need for a radioisotope generator, which makes this imaging test more accessible to patients across the country in any nuclear medicine facility with PET imaging capability.
e. Reduces patient healthcare cost by eliminating the requirement for patient presence at a limited number of designated centers providing ^{68}Ga based NET imaging agents.

Two prior studies were conducted with ^{64}Cu-DOTATATE. The first was a retrospective analysis of a study of the use of ^{64}Cu-DOTATATE for the detection of somatostatin receptor-positive neuroendocrine tumors. The primary objective of the study was to investigate whether ^{64}Cu-DOTATATE PET scan findings had the ability to diagnose somatostatin receptor-positive NETs. The study results were previously published (Pfeifer, 2012: Pfeifer, 2015). The secondary objective of the study was to evaluate the PPV, NPV, and accuracy of ^{64}Cu-DOTATATE PET scan findings relative to the SOT. The second study was an open-label, single-dose, dose-ranging study with a primary objective to identify the lowest amount of administered dose to obtain a diagnostic quality ^{64}Cu-DOTATATE PET-CT scan for imaging patients with known somatostatin receptor-positive NETs, coincident with the as low as reasonably achievable (ALARA) principle. The secondary objective of this study was to assess the effect of ^{64}Cu-DOTATATE dose on PET-CT image quality. Reports for both of these studies are final and available upon request. The four subjects who received the selected dose in the dose ranging study are included in the analysis presented in this report.

8 STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective of this study was to assess the performance (sensitivity and specificity) of ^{64}Cu-DOTATATE PET-CT imaging in subjects with known or suspected NETs, when comparing individual reader results to a standard of truth (SOT) for each subject.

8.2 SECONDARY OBJECTIVES

The secondary objectives of this study were as follows:

- To characterize the predictive value of ^{64}Cu-DOTATATE PET-CT imaging when comparing an imaging reader-majority rule determination to the SOT for each subject and also when the comparison was performed on an individual reader basis.
- To evaluate the imaging performance (sensitivity and specificity) of ^{64}Cu-DOTATATE when comparing an imaging reader-majority rule determination to the SOT for each subject.
- To evaluate the imaging performance of ^{64}Cu-DOTATATE to determine if subjects had metastatic or local disease as compared to the SOT.

8.3 TERTIARY OBJECTIVE

The tertiary objective of this study was to evaluate the intra-reader and inter-reader agreement.

8.4 EXPLORATORY OBJECTIVE

The exploratory objective of this study was to evaluate pharmacokinetics and identify any major ^{64}Cu moieties other than intact parent drug (^{64}Cu-DOTATATE), free ^{64}Cu, and known radiolysis byproducts of the parent drug.

9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This was an open-label, single-dose, single-arm, single-center non-comparative study using DOTATATE peptide, labeled with the ^{64}Cu tracer to assess imaging performance versus standard of truth (SOT).

The imaging dose was identified in a phase 1 study. PET/CT imaging started 60 ± 15 minutes after injection for all subjects. The study recruited, enrolled, and investigated subjects comprising healthy volunteers as well as patients with confirmed or suspicious for NETs based on histopathology and/or by anatomical and/or functional imaging and/or blood tumor markers for NETs.

For safety assessment, vital signs were measured within 30 minutes before and for up to 1 hour after administration of ^{64}Cu-DOTATATE. A blood sample was collected within 30 minutes before the injection and within 2 hours post ^{64}Cu-DOTATATE administration for assessing clinical chemistries and haematology.

Any adverse events observed or reported were recorded for up to 48 hours following study drug administration. In addition, observed or patient reported immediate adverse events including but not limited to pain, injection site reaction, headache, nausea, vomiting, flushing or other as reported, were assessed within 1 hour before and within 2 hours after the study drug administration.

All subjects underwent a continuous ECG recording at least 15 minutes prior to administration of the study drug 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 study drug administration. All the ECG data were collected in digital format, analysed and reviewed (with manual over-read) by an independent (i.e., not otherwise affiliated with the study) physician expert to assess the recordings as normal or abnormal and whether clinically significant or not significant.

To assess pharmacokinetics, blood and urine samples were collected after the administration of ^{64}Cu-DOTATATE on 6 subjects. Five 10 mL blood samples were collected at 1, 10, 30, 60, and 120 minutes after the administration of ^{64}Cu-DOTATATE. Urine samples were collected in three intervals after the administration of ^{64}Cu-DOTATATE; 0-60 minutes, 60-120 minutes, and 120-360 minutes. The pharmacokinetic (PK) analysis was focused only on radiometric detection using a bioanalytical high performance liquid chromatography (HPLC) method.

9.1.1 Screening Visit

9.1.1.1 Patients

- Written informed consent
- Demographic information
- Relevant medical history and concomitant medications
- Vital signs
- Histology and/or clinical information reports
- Anatomical and functional imaging studies information

- Urine or Blood Pregnancy test, if applicable

9.1.1.2 Healthy Volunteers

- Written informed consent
- Demographic information
- Relevant medical history
- Vital signs
- Physical Exam
- ECG Exam
- Anatomical imaging studies information
- Urine or Blood Pregnancy test, if applicable
- Illicit drug screening questionnaire
- Concomitant medication information

9.1.2 Injection Visit

Once all screening/baseline procedures were performed, the following procedures were completed on the day of injection. In the event multiple tasks needed to be performed at the same time or within a short time frame, every effort was made to complete all tasks back to back in the most efficient way.

9.1.2.1 Pre-dose and Dosing Procedures

- Pre-dose vital signs – within 30 minutes before dose
- Pre-dose observed or patient reported immediate adverse drug reactions – within 1 hour before dose
- Pre-dose blood sample collection- within 30 minutes prior to study drug injection
- Pre-dose static ECG recording - within 60 minutes prior to study drug injection
- Pre-dose continuous ECG recording - within 15 minutes prior to study drug injection
- Pre-dose Urine Pregnancy test, if applicable
- Injection of study drug ^{64}Cu-DOTATATE
- Start recording adverse events

9.1.2.2 Post-dose Procedures

- Post-dose vital signs– 5, 10, 30, 60 minutes and discharge
- Post-dose observed or patient reported immediate adverse drug reactions – up to 2 hours after dose
- Post-dose blood sample collection- within 2 hours ± 30 minutes
- Post-dose blood sample collection for PK analysis, for 6 subjects only – 1, 10, 30, 60, and 120 minutes after study drug administration

- Post-dose urine sample collection for PK analysis, for 6 subjects only – collected over the following intervals: 0-60 minutes, 60-120 minutes, and 120-360 minutes after study drug administration
- Post-dose static ECG recording - within 60 minutes after study drug administration
- Post-dose continuous ECG recording - Continuous 30 minutes after study drug administration
- Whole-body PET/CT from top of the skull to mid-thigh region.
- Recording of adverse events up to 48 hours post injection

9.1.3 Follow-Up

<u>24 ± 4 hours telephone follow-up</u>

- Adverse events
- Patient reported symptoms

<u>48 ± 4 hours telephone follow-up</u>

- Adverse events
- Patient reported symptoms

<u>Day 1-2 post-injection follow-up</u>

- Blood Sample for Clinical Laboratory tests

9.2 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUP

The study followed a standard imaging accuracy/efficiency evaluation design. The imaging sensitivity, specificity, accuracy and predictiveness of the study drug were assessed using a predefined standard of truth (SOT) parameter. A conventional scan, such as an anatomical imaging modalities CT, and MRI or functional imaging using OctreoScan®, ^{68}Ga-DOTATATE ^{18}F-FDG and NaF PET/CT or bone scan along with clinical data composed a key part of the SOT, which were determined by an oncologist. ^{64}Cu-DOTATATE images were independently interpreted by readers blinded to all clinical information for the subjects, including the results of any other imaging modalities. The primary endpoint required two out of three of the readers exceeding the pre-specified sensitivity and specificity thresholds. This design aligned with contemporary precedent for important imaging studies and provided a solid assessment of ^{64}Cu-DOTATATE performance. The study was a single-arm clinical trial and did not include a control group.

9.3 SELECTION OF STUDY POPULATION

The study population was comprised of both healthy volunteers, as required by the SAP and agreed upon by the FDA in the pre-IND meeting, and patients confirmed or suspicious for NETs. The EE population consisted of all subjects who were enrolled in the study and 4 subjects from the selected 4.0 mCi dose cohort of the Phase 1 study having the following characteristics: had an established SOT, were injected with ^{64}Cu-DOTATATE, and had an image read result using ^{64}Cu-DOTATATE by three independent readers. This sample size was appropriate to achieve

statistical power for the primary endpoints of this clinical trial. The subjects were recruited at the clinical site, Excel Diagnostics and Nuclear Oncology Center located at 9701 Richmond Ave., Houston, TX 77042.

9.3.1 Inclusion Criteria

Subjects were eligible to participate in the study if they met all of the following inclusion criteria:

9.3.1.1 Patients

1. Subjects of either sex, aged ≥18 years.
2. Met at least one of the following criteria:
    a. Confirmed or suspicion of NET based on histology/biopsy report.
    b. Confirmed or suspicion of NET based on conventional imaging scans of affected area such as MRI and/or contrast enhanced CT and/or FDG PET-CT scan and/or NaF PET-CT scan and/or OctreoScan® performed within 8 weeks prior to study date.

9.3.1.2 Healthy Volunteers

Healthy male or female subjects aged ≥18 years of age and in good health as determined by absence of clinically relevant abnormalities determined by a full medical history, physical examination, vital signs and clinical laboratory tests.

9.3.1.3 Patients and Healthy Volunteers

1. Willing to sign informed consent form.
2. Able to understand and comply with the procedures and requirements of the study.
3. Negative pregnancy test in women of child-bearing potential, performed within 48 hours prior to the study drug injection, using urine or blood-based testing.
4. For women of childbearing potential, agreement to remain abstinent (refrain from heterosexual intercourse) or use non-hormonal contraceptive methods for at least 2 weeks following administration of study drug.
5. For men, agreement to remain abstinent (refrain from heterosexual intercourse) for at least 2 weeks following administration of study drug or use contraceptive measures.
6. Recent blood test results (within 4 weeks pre-dose) as follows:
    a. WBC: $>2\times10^9$/L
    b. Haemoglobin: >8.0g/dL
    c. Platelets: $>50\times10^9$/L
    d. ALT, AST, AP: ≤5 times ULN
    e. Bilirubin: ≤3 times ULN
    f. Serum creatinine: <170 μmol/L

9.3.2 Exclusion Criteria

Subjects were excluded from study participation if they met any of the following exclusion criteria:

1. Pregnant or planning to become pregnant within the next two weeks.
2. Inability to provide written consent.
3. Therapeutic use of any somatostatin analogue, including Sandostatin® LAR (within 28 days) and Sandostatin® (within 2 days) prior to study imaging. If a subject was on Sandostatin® LAR, a wash-out period of 28 days was required before the injection of the study drug.
4. History or presence of significant hematological abnormalities or immunodeficiency or any condition that might compromise the immune system (infection, vaccination), or any etiology as indicated by clinically significant abnormal values of any of the following hematologic parameters: platelets, hemoglobin, WBC count and ANC.
5. Lactating and breast-feeding women.
6. Acute or chronic clinically significant conditions such as uncontrolled congestive heart failure, liver or kidney dysfunction, uncontrolled hypertension.
7. History of hypersensitivity to drugs with a similar chemical structure to the investigational product or any of its excipients.
8. History of significant drug abuse within 1 year prior to screening or use of soft drugs (such as marijuana) within 3 months prior to the screening visit or hard drugs (such as cocaine, phencyclidine, and crack) within 1 year prior to screening.
9. Participation in other clinical research trials involving evaluation of other investigational treatments within 30 days prior to enrollment and/or unwilling to allow at least one week before participation in another drug trial following the current study.

9.3.3 Removal of Subjects from Study Participation

The investigator could withdraw a subject from the trial for any of the following reasons:

- Protocol violation,
- Serious or intolerable adverse event (that in the opinion of the investigator, required the subject's discontinuation; still, all adverse events were followed until resolution or stabilization to a non-clinically significant state),
- Investigator withdrew the subject (at the investigator's discretion for reasons other than an adverse event),
- Sponsor terminated the study, or
- Subject requested to be discontinued from the study,

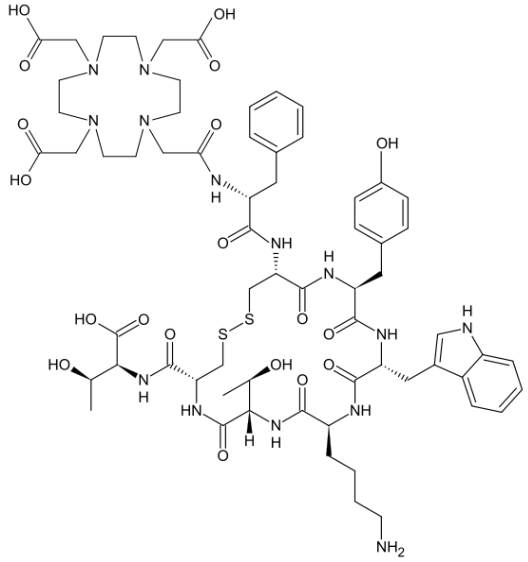
The investigator documented the reason(s) for any subject withdrawal in the CRF.

9.4 TREATMENTS

9.4.1 Study Drug Administered

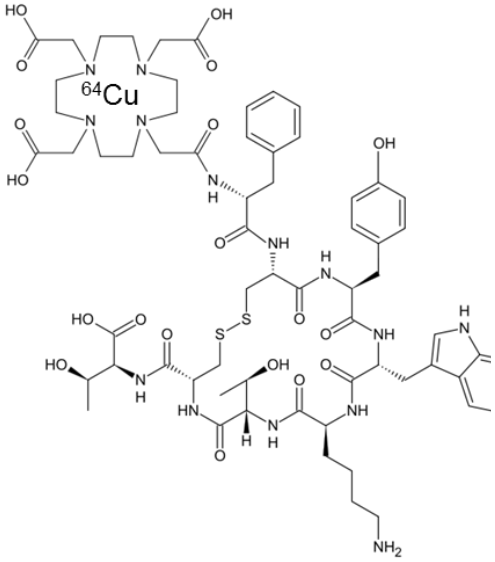
Chemical name and structure:

DOTATATE (Precursor)



^{64}Cu Cl_2 →

^{64}Cu-DOTATATE (Drug Product)



The study drug is "Copper" ^{64}Cu-DOTATATE, where ^{64}Cu (the tracer) is a positron-emitter, Octreotate (the peptide) is a somatostatin analogue, and DOTA (chelator) is a chemical chelator used to link ^{64}Cu to Octreotate.

^{64}Cu-DOTATATE: Copper(1-), [N-[[4,7,10-tris[(carboxy-κ O)methyl]-1,4,7,10-tetraazacyclododec-1-yl-κ N1,κ N4,κ N7,κ N10]acetyl-κ O]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-threonine cyclic (2→7)-disulfidato(4-)]

Molecular weight: 1497.2 g/mol

Route of administration: intravenous.

Composition: A unit dose of ^{64}Cu-DOTATATE contains the ingredients listed in Table 1:

Table 1: Composition of ^{64}Cu-DOTATATE Injection Solution

Name of ingredient(s)	**Quantity per Unit dose**	**Function**
^{64}Cu-DOTATATE	4.0 mCi ± 10%	Active pharmaceutical ingredient
DOTATATE	< 100 µg	Active pharmaceutical ingredient
Sodium Ascorbate	4.5% (w/v)	Buffer and Stabilizer
Gentisic Acid	< 0.02% (w/v)	Buffer and Stabilizer
Ethanol	5% (v/v)	Stabilizer

Sterile Water for injection	95% (v/v)	Solvent

^{64}Copper is a positron-emitting isotope with an intermediate half-life (12.7 hours), produced in a cyclotron by bombarding proton beams to an enriched ^{64}Ni target to produce a ^{64}Ni(p,n) ^{64}Cu nuclear reaction. The main advantage of Cu-64 is that it can be produced in large quantities in a centralized facility. Its intermediate half-life also allows shipment of radiolabeled unit doses to end-users. Furthermore, the non-halogenated and non-volatile chemical properties of ^{64}Cu make this isotope ideal as a PET tracer. Other key radiochemical characteristics of ^{64}Cu are summarized in Table 2.

Table 2: Radiochemical characteristics of ^{64}Cu isotope

^{64}Cu physical half-life T½	**Decay product**	**Maximum positron energy**	**Maximum linear range**
12.7 hrs	^{64}Ni (61%) ^{64}Zn (39%)	0.66 MeV	1.0 mm

9.4.1.1 Study Drug Dosing and Schedule

The study drug was administered as an intravenous bolus injection. Injection was given by hand directly into a 22 or 24-gauge catheter at a rate of 3-4 mL/min and the catheter was flushed with 3 mL of normal saline post-injection. The radioactivity/dose was measured before and after injection using a calibrated machine and recorded. The difference in radioactivity before the injection and after injection was considered as the total injected dose. A 10 mL, sterile, single use syringe was used to administer the test drug and a 10 mL, sterile, single use syringe was used to flush the catheter port with normal saline.

9.4.2 Identity of Investigational Product(s)

The ^{64}Cu-labeled radiopharmaceuticals were produced at a centralized production facility. The production of Cu-64 and radiolabeled ^{64}Cu-DOTATATE drug product was manufactured at RadioMedix Inc. The radiolabeled drug product underwent radiopharmaceutical quality control tests, as specified in the chemistry manufacturing and control (CMC) document. A unit dose of ^{64}Cu-DOTATATE drug product calibrated to time of use was dispensed into a sterile vial and shipped to the study site.

^{64}Cu-DOTATATE drug product was prepared according to Current Good Manufacturing Practice (cGMP) per U.S. Food and Drug Administration (FDA) guidelines. Production was performed at RadioMedix Inc., located at 9701 Richmond Ave, Suite: 222 Houston, Texas 77042.

9.4.3 Method of Assigning Subjects to Treatment Groups

This was a single-arm study. All subjects received the same treatment.

9.4.4 Selection of Doses in the Study

The optimal dose of ^{64}Cu-DOTATATE was determined by the dose ranging study to be 4 mCi administered as an intravenous bolus injection.

9.4.5 Selection and Timing of Dose for Each Subject

The duration of subject participation was from the time of signing the informed consent form through the 2-day post-injection visit. A subject was deemed enrolled in the study once the subject signed the informed consent form.

Each subject received a one-time dose of radiolabeled ^{64}Cu-DOTATATE drug product. Subjects followed their normal diet before and after the administration of the study drug. Subjects were encouraged to increase fluid intake at baseline and after image acquisition to maintain proper hydration throughout the study period and decrease radiation exposure to the urinary bladder. To enhance imaging, subjects were encouraged to void prior to study imaging, post-injection. There were no dietary, food, or activity restrictions for this study.

9.4.6 Prior and Concomitant Therapy

All prior and concomitant medications taken by or administered to a subject in the safety population were collected from the 30 days prior to informed consent until completion/withdrawal from the study. Concomitant medications were coded using the WHO Drug Dictionary. A data listing for concomitant medications for all safety subjects was provided.

9.4.7 Treatment Compliance

All study drug administration was done under the supervision of the principal investigator. Details of study drug injection were captured in each subject's source documents.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

The following sections define the efficacy and safety assessments that were performed during the study. The schedule of events is summarized in Table 9.5.1-1.

Table 9.5.1-1: Study Schedule and Flow Chart

		Study Day						Follow up		
Evaluation/ Procedure	**Screening Within 14 days of injection**	**Day 1**						**Day 2 (24 ± 4 hr)**	**Day 3 (48 ± 4 hr)**	**Day 1-2**
		Pre-study drug administration (within)		**Study drug injection**	**Post-study drug administration (within)**					
		60 min	**30 min**	**0 min**	**30 min**	**60 min**	**120 min / Discharge**			
Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Demographics	X									
Medical/Surgical History	X									
Physical exam (healthy volunteers only)	X									
Concomitant Medications	X									
Urine or blood Pregnancy Test (females only) if applicable [j]	X									
SOT imaging report[a]	X									
Screening Lab Tests [b]	X									
Illicit drug screening questionnaire	X									
Vital Signs [c]	X		X [c]		X [c]	X [c]	X [c]			
12-lead static ECG [i]	X	X				X				
Study drug administration				X						
Observed or patient reported immediate drug reactions [d]		X [c]					X [c]			
Clinical Laboratory Tests [e]			X				X			X
12-Lead continuous Electrocardiogram			X [f] start		X [f] stop					

		Study Day						Follow up		
Evaluation/ Procedure	**Screening Within 14 days of injection**	**Day 1**						**Day 2 (24 ± 4 hr)**	**Day 3 (48 ± 4 hr)**	**Day 1-2**
		Pre-study drug administration (within)		**Study drug injection**	**Post-study drug administration (within)**					
		60 min	**30 min**	**0 min**	**30 min**	**60 min**	**120 min / Discharge**			
Adverse Events [g]		X start							X stop	
Post -study drug imaging [h]						X				
Blood sample collection for PK analysis					X [k]	X [k]	X [k]			
Urine sample collection for PK analysis						X [l]	X [l]			

Schedule of Events Footnotes

a) SOT images/report within 8 weeks.
b) Screening lab and other relevant clinical information within 4 weeks.
c) Vital signs (blood pressure, body temperature, respiratory rate, and pulse rate) were collected pre-dose (within 30 minutes) and 5, 10, 30, 60, and at the time of discharge post ^{64}Cu-DOTATATE injection.
d) Observed or patient reported immediate adverse drug reactions (pain, injection site reaction, headache, nausea, vomiting, flushing, or other) were collected pre-dose (within 1 hour) and post ^{64}Cu-DOTATATE injection (within 2 hours).
e) Blood sample collection for clinical laboratory assessments (including hematology and clinical chemistry) within 30 minutes pre-dose, within 2 hours and within 1-2 days post-dose.
f) Continuous ECG monitoring was performed for at least 15 minutes pre-dose and 30 minutes after study drug administration.
g) Adverse events were collected pre-dose (within 1 hour) and post ^{64}Cu-DOTATATE injection (within 2 hours), and a follow-up by phone at 48 hours.
h) Post study drug imaging times were ± 15 minutes.
i) For healthy volunteers only.
j) Urine dip stick on the day of injection or blood based pregnancy test within 48 hours
k) Blood sample collection for PK analysis, on 6 subjects only – 1, 10, 30, 60, and 120 minutes after study drug administration.
l) Urine sample collection for PK analysis, on 6 subjects only – 0-60 minutes, 60-120 minutes, and 120-360 minutes after study drug administration.

*In the event multiple tasks needed to be performed at the same time or within a short time frame, every effort was made to complete all tasks back to back in the most efficient way.

9.5.1.1 Efficacy Assessments

The co-primary effectiveness endpoints of the study were assessed by the sensitivity and specificity of ^{64}Cu-DOTATATE when comparing individual reader results relative to the SOT.

9.5.1.2 Safety Assessments

Safety was primarily assessed through treatment emergent adverse events (TEAEs). An AE was considered treatment emergent if the start date and time were on or after the start date and time of the injection of study drug. If the AE had a missing start date or time, or if the injection start time was unknown, then the event was considered treatment emergent.

Adverse events (AEs) were monitored for each subject from the time of enrollment to exit from the study. AEs that were collected from the time of informed consent to immediately before injection were recorded in the medical history. Vital signs were recorded on each subject at 30 minutes pre-injection (baseline) and within 1-hour post-injection. Clinical laboratory parameters were obtained from blood samples taken at 30 minutes prior to injection and at the Day 1-4 Follow-up visit. A 12-lead ECG reading was taken 30 minutes prior to injection and within 2 hours post-injection.

9.5.1.3 Pharmacokinetic Assessments

To assess pharmacokinetics, blood and urine samples were collected after the administration of ^{64}Cu-DOTATATE on 6 subjects. The PK analysis was focused only on radiometric detection using a bioanalytical HPLC method.

The PK assessment was performed as recommended by the FDA during the October 4th, 2016 PIND meeting. Blood samples were analyzed at 1, 10, 30, 60, and 120 minutes. Urine samples were analyzed in three intervals post-injection of the study drug (^{64}Cu-DOTATATE); 0-60 minutes, 60-120 minutes, and 120-360 minutes. The rationale for selecting these timepoints to assess PK characteristics was based on the PK reports of ^{177}Lu-DOTATATE (Esser, 2006). Radioactivity is rapidly cleared from the plasma leaving <10% of the injected dose in the blood at 3 hours after administration and half of the injected dose is recoverable in the urine within six hours post-injection.

The PK assessment was exploratory in nature. Results of the PK assessment are presented in Section 16.1.11.

9.5.2 Appropriateness of Measurements

The efficacy and safety assessments are widely used and generally recognized as reliable, accurate, and relevant.

9.5.3 Primary Efficacy Variables

The co-primary effectiveness endpoints were the sensitivity and specificity of ^{64}Cu-DOTATATE PET-CT imaging when each imaging reader's subject-level result was compared to a SOT for the subject, with primary endpoint success defined as the same two out of three readers having sensitivity and specificity results exceeding the specified thresholds.

9.5.4 Secondary Efficacy Variables

The secondary effectiveness endpoints of the study were:

- majority of readers sensitivity
- majority of readers specificity
- majority of readers positive predictive value (PPV)
- majority of readers negative predictive value (NPV)
- majority of readers accuracy
- individual reader sensitivity and specificity in distinguishing between localized and metastatic disease
- majority reader sensitivity and specificity in distinguishing between localized and metastatic disease
- individual reader accuracy, PPV, and NPV

9.5.5 Tertiary Efficacy Variables

The following tertiary effectiveness endpoints of the study evaluated the variability between readers as well as the variability within readers using repeat reads of selected images:

- intra-reader agreement using Cohen's Kappa
- inter-reader agreement using Cohen's Kappa

Agreement was assessed across the categories of "Localized Disease", "Metastatic Disease", and "No Disease". Agreement among the 3 readers was assessed using Fleiss's generalized Kappa.

9.5.6 Safety Variables

The following safety variables were measured in this trial:

- Adverse events
- Vital signs
- Clinical laboratory parameters
- ECG Recordings

9.5.7 Drug Concentration Measurements

The radioactivity/dose was measured before and after injection using a calibrated machine and recorded. The difference in radioactivity before the injection and after the injection was considered as the total injected dose.

9.6 DATA QUALITY ASSURANCE

The study site was chosen with regard to the capability and expertise of the principal investigators and the site staff. Prior to initiation of the study, the investigator and the sponsor's representative met to discuss the study design and conduct of the study. The investigator signed

the protocol acknowledging that he understood the design and all procedures and intended to conduct the study and all procedures according to protocol.

During the study, a representative of the sponsor made periodic visits to the investigational site while the study was in progress to check the accuracy and completeness of the data being entered. Site visits were conducted to inspect study data, subjects' medical records, and eCRFs in accordance with ICH guidelines, GCPs, and the respective local and national government regulations and guidelines. The investigator permitted authorized representatives and the respective local and national health authorities to inspect facilities and records relevant to this study, if needed.

Subject data was collected on source documents and entered in the eCRF. Data was reviewed and validated. The investigator signed and dated a declaration on the eCRF attesting to his/her responsibility for the quality of all data recorded and that the data represents a complete and accurate record of each subject in the study.

Records of subjects, source documents, monitoring visit logs, inventory of study product, regulatory documents (e.g., protocol and amendments, IRB/IEC correspondence and approvals, approved and signed informed consent forms, Investigator's Agreement, clinical supplies receipts, and distribution and return records), and other sponsor correspondence pertaining to the study were kept in the appropriate study files at the site. Source documents included all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. At the end of the study, eCRF data was provided to the investigator.

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical Plans

9.7.1.1 Analysis Populations

The following analysis populations were defined:

Efficacy Evaluable (EE) Population – The EE population consisted of all subjects who were enrolled in the phase 3 study and 4 subjects from the selected 4.0 mCi dose cohort of the Phase 1 study having the following characteristics:

- had an established SOT;
- were injected with ^{64}Cu-DOTATATE; and
- had an image read result using ^{64}Cu-DOTATATE by three independent readers.

Safety Population – The safety population consisted of all subjects who were enrolled in the study and had been injected with ^{64}Cu-DOTATATE.

The EE population was used for the primary analysis of all effectiveness analyses. The safety population was used for the analysis of all safety variables and baseline characteristics.

9.7.1.2 General Statistical Methodology

The data analyses were conducted using SAS© Software, Version 9.4 or higher.

9.7.1.2.1 Disposition and Demographics

The continuous demographic characteristics at screening (age, height, and weight) were summarized for all subjects in the safety population using descriptive statistics (mean, standard deviation, median, minimum, maximum, and number of non-missing observations). The categorical baseline characteristics (gender, race, ethnicity) were summarized for the safety population using frequency counts and percentages. Detailed listings of all baseline and demographic data for each subject are provided.

9.7.1.2.2 Protocol Deviations

Protocol violations/deviations were documented by the investigator and submitted to the IRB/IEC, as required by IRB/IEC requirements.

9.7.1.2.3 Medical History

A table was constructed with counts and percentages of the number of subjects who were normal/abnormal by body system. A data listing for medical history information for all safety subjects is provided.

9.7.1.2.4 Extent of Exposure and Treatment Compliance

A table was constructed to summarize ^{64}Cu-DOTATATE dosing for the safety population in this study. Summary statistics (mean, standard deviation, n, minimum, maximum and median) were computed on the wand counts on the dosing unit both pre and post injection and on the dose volume. A data listing for dosing information for all safety subjects is provided. A summary of ^{64}Cu-DOTATATE dose administration is displayed in Section 12.1 of this report.

9.7.1.2.5 Safety Analysis

The following safety analyses were conducted on the safety population.

Adverse Events

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Safety was primarily assessed through treatment emergent adverse events (TEAEs). An AE was considered treatment emergent if the start date and time was on or after the start date and time of the injection of study drug. If the AE had a missing start date or time, or if the injection start time was unknown, then the event was considered treatment emergent.

TEAEs were summarized by the total number and by the number and proportion of subjects reporting at least one occurrence of the TEAE. Frequencies of each TEAE were summarized by MedDRA preferred term within system organ class (SOC) and by severity, relation to study drug, and time of onset (before or after the initiation of study drug). Frequencies of each SAE were summarized by total number, by the number and proportion of subjects reporting at least one occurrence of the SAE, and by MedDRA preferred term within system organ class (SOC).

Vital Signs

For each vital sign parameter, summary statistics on the raw and change from baseline values at each time point were calculated. If multiple vital signs were recorded for a given time point, then the most recent results from each time point were used in the analysis.

Clinical Laboratory Parameters

For each quantitative clinical laboratory parameter, summary statistics on the raw and change from baseline values at each time point were calculated. If multiple pre-injection labs were recorded, then the results closest to imaging were used as baseline.

ECG Parameters

A shift table was constructed to show the shifts in ECG interpretations between the pre-dose recording and the post-dose recoding. The number and percentage of subjects with the following shifts were presented: normal/normal, normal/abnormal, abnormal/normal, and abnormal/abnormal.

9.7.1.2.6 Analysis of Efficacy Data

9.7.1.2.6.1 Analysis of Primary Efficacy Endpoints

The following two-way table was utilized to compute sensitivity, specificity, NPV, PPV, and accuracy:

		SOT Reference Standard	
		Disease	No Disease
^{64}Cu-DOTATATE Scan Result	Disease	TP	FP
	No Disease	FN	TN

Based on the above, the co-primary effectiveness endpoints were computed as follows for each reader:

- sensitivity = TP/(TP + FN)
- specificity = TN/(TN + FP)

The following two hypotheses were tested at the end of the study relative to the co-primary endpoints:

$$H_{a0}: \text{Sensitivity} \leq 70\% \text{ vs } H_{a1}: \text{Sensitivity} > 70\%$$

and

$$H_{b0}: \text{Specificity} \leq 60\% \text{ vs } H_{b1}: \text{Specificity} > 60\%$$

Each hypothesis test was conducted at the one-sided $\alpha = 0.025$ level of significance. Point estimates of sensitivity and specificity were calculated along with two-sided 95% confidence intervals using the score method. The sensitivity and specificity were calculated on a by-reader basis. Success upon the primary endpoints was declared if two of the three independent readers achieved sensitivity and specificity results in excess of the thresholds designated above. That is, the same two out of three readers achieved success upon sensitivity and specificity.

9.7.1.2.6.2 Analysis of Secondary Efficacy Endpoints

Based on the table presented above, the secondary effectiveness endpoints were computed as follows:

- NPV = TN/(TN + FN)
- PPV = TP/(TP + FP)
- accuracy = (TP + TN)/(TP + TN + FP + FN)

The above endpoints were computed using the majority read (i.e., majority ^{64}Cu-DOTATATE diagnosis from the 3 readers) as well as by reader. Point estimates of the majority read and by reader NPV, PPV, and accuracy were calculated along with 95% confidence intervals using the score method.

Readers who identified an image as positive were asked to further classify the disease as localized or metastatic. Sensitivity and specificity were determined relative to the SOT.

In addition, majority sensitivity and specificity were computed as secondary effectiveness endpoints. Point estimates were calculated along with 95% confidence intervals using the score method.

9.7.1.2.6.3 Analysis of Tertiary Efficacy Endpoints

For each reader pair (Readers 1&2, Readers 1&3, and Readers 2&3), a Cohen's Kappa along with a 95% confidence interval on Cohen's Kappa was computed. A Generalized Fleiss Kappa and associated 95% confidence interval was computed to assess overall agreement among the 3 readers.

Intra-reader variability was assessed using the n=7 randomly chosen study images that were re-read by the readers. Cohen's Kappa was computed for each reader on the pairs of re-reads for each image. A 95% confidence interval on Cohen's Kappa was computed. A generalized Kappa and 95% confidence interval was computed in order to assess overall intra-reader reliability.

9.7.1.2.7 Pharmacokinetic Analysis

Analysis of the PK data are provided in a separate PK report, included in Appendix 16.1.11 of this report.

9.7.2 Determination of Sample Size

The study was powered with respect to the co-primary endpoints of sensitivity and specificity.

In order to have at least a 90% chance of showing that the sensitivity was at least 0.70 and the specificity was at least 0.60 a sample of 63 subjects was needed, divided among $n_1 = 42$ SOT positive subjects and $n_2 = 21$ SOT negative subjects. This sample size was derived under the assumptions that the readers were viewing the same images and that their reads were correlated at r = 0.70 and that the true Sensitivity and Specificity are each 0.90. The study was powered at 90% for each subtest to give the overall study 80% power.

This sample size was determined by Monte Carlo simulation with the parameter values given above. The simulation used 5000 replications: the standard error of the estimated power was no

more than 0.6%. To satisfy the sample size requirements for each endpoint a total of n=63 subjects was needed, allocated in a 2:1 (Positive:Negative) ratio.

These calculations assumed a one-sided α=0.025 level of significance and that the data came from a binomial distribution.

PK Analysis Sample Size:

The PK assessment was performed on 6 subjects as an exploratory study.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Intra-reader variability was planned to be assessed using n=10 randomly chosen study images that were re-read by the readers. This was interpreted by World Care Clinical to mean n=10%, thus n=7 randomly chosen study images were ultimately re-read by the readers.

The SAP and protocol planned for the creation of 20 clinical laboratory shift tables. Data in the clinical database allowed for the creation of 30 clinical laboratory shift tables. The additional, unplanned shift tables include albumin, calcium, carbon dioxide, chloride, glucose, potassium, protein, and sodium. Furthermore, the SAP planned a combined data table for shifts in mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, and mean corpuscular volume. The finalized tables include separate shift tables for these parameters.

There was a discrepancy between the SAP and the protocol regarding the following items: injection of radioactivity, waiting time allowed for tracer distribution, and PET scan acquisition time. The SAP required an injection of 185-227 MBq (5.0-6.0 mCi) of ^{64}Cu-DOTATATE followed by a 20 minute PET scan beginning 50 minutes post-injection. The protocol required an injection of 148 ± 10% MBq (4.0 ± 10% mCi) of ^{64}Cu-DOTATATE followed by a 5 minute per bed position PET scan beginning 60 ± 15 minutes post-injection. The protocol was followed during the clinical study.

^{68}Ga-DOTATATE PET-CT reports were included in the clinical data package that was presented to the independent oncologist in order to establish the SOT as ^{68}Ga-DOTATATE is the new gold standard for somatostatin receptor positive NET tumors. The revised SOT is therefore defined as follows: confirmed or suspicious NET disease by histology or conventional anatomical and/or functional imaging modalities including but not limited to magnetic resonance imaging (MRI), computed tomography (CT), F-18 FDG PET-CT, F-18 NaF bone PET-CT, bone scintigraphy, and/or Octreoscan®, and/or ^{68}Ga-DOTATATE PET-CT. This SOT is the SOT used in the analysis.

10 STUDY SUBJECTS

10.1 DISPOSITION OF SUBJECTS

A total of 68 subjects were screened for this study. Of these, 66 were enrolled, including 4 subjects from the 4.0 mCi dose cohort from the Phase 1 study. A total of 63 subjects (95.5%), 59 from the Phase 3 study and 4 from the Phase 1 study cohort, completed the study. Three subjects (4.5%) withdrew consent prior to receiving study treatment.

Subject disposition of all screened subjects is presented in Table 10.1-1.

Table 10.1-1: Subject Disposition (All Screened Subjects)

	Overall
Screen Failure	2
Enrolled	66
Completed	63 (95.5%)
Early Termination (Withdrawal)	3 (4.5%)
Reason for Early Termination (Early Withdrawal)	
Death	0 (0.0%)
Adverse Event	0 (0.0%)
Lost to Follow Up	0 (0.0%)
Withdrawal of Subject Consent	3 (4.5%)
Investigator Discretion	0 (0.0%)
Protocol Deviation	0 (0.0%)
Sponsor Discretion	0 (0.0%)
Other	0 (0.0%)

Source: Data Table 1

10.2 PROTOCOL DEVIATIONS

The only protocol deviations noted in this study involved violations of the inclusion/exclusion criteria. A total of 5 subjects grouped as NET positive violated the inclusion criteria of having a confirmed or suspicion of a NET based on histology/biopsy report. Additionally, one subject, subject NET3-SC-0005, was screened but violated the inclusion criteria of being able to understand and comply with the procedures and requirements of the study and another screened subject, subject NET3-SC-0002, violated the exclusion criteria of having a history of significant drug abuse within 1 year prior to screening or use of soft drugs within 3 months prior to the screening visit or hard drugs within 1 year prior to screening. Consequently, these two subjects were screen failures and not enrolled in the study.

PET/CT images were acquired outside of the protocol time window for 8 subjects. These deviations ranged from 6 minutes earlier to 22 minutes later than the protocol requirement of 60 ± 15 minutes (45-75 minutes). A complete listing of PET-CT image acquisition deviations is provided in Appendix 16.1.13. Blood draws were performed outside of the protocol time window for 7 subjects. A complete listing of clinical laboratory deviations is provided in Appendix 16.1.13.

11 EFFICACY EVALUATION

11.1 DATA SETS ANALYZED

The efficacy evaluable (EE) population was used for the primary analysis of all effectiveness analyses. The EE population consisted of all subjects who were enrolled in the study and 4 subjects from the selected dose cohort of the Phase 1 study having the following characteristics: had an established SOT, were injected with ^{64}Cu-DOTATATE, and had an image read result using ^{64}Cu-DOTATATE by three independent readers.

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and other baseline characteristics for the safety population are presented in Table 11.2-1. The median age of all enrolled subjects was 54 years. Subjects ranged in age from 25 to 82 years. The mean (SD) age of all subjects was 54.37 (15.65) years and the mean (SD) weight was 185.75 (46.70) pounds. 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 safety population. The remaining subjects were Asian (3.2%) or other (1.6%).

A by-subject listing of demographics is provided in Data Listing 6. Of note, subject 051 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).

A total of 47 subjects (74.6%) reported at least 1 medical history event. The most common medical history events included vascular disorders (39.7%), metabolism and nutrition disorders (28.6%), gastrointestinal disorders (23.8%), psychiatric disorders (22.2%), and endocrine disorders (17.5%).

A summary of medical history findings is provided in Data Table 4. A by-subject listing of medical history is provided in Data Listing 12.

Table 11.2-1: Demographics and Baseline Characteristics (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: Data Table 2 & Data Table 3

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Injection of ^{64}Cu-DOTATATE was performed at the study site under the supervision of the investigator. A total of 63 subjects were injected with a mean dose of 4.11 mCi of ^{64}Cu-DOTATATE. A total of 62 subjects received a dose of 4 mCi ± 10% of ^{64}Cu-DOTATATE. Subject AA-NET3-006 received a total injected dose of 3.5756 mCi of ^{64}Cu-DOTATATE.

A by-patient listing of drug administration is provided in Data Listing 14.

11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL SUBJECT DATA

11.4.1 Analysis of Efficacy

By-patient listings of primary and secondary efficacy are provided in Data Listing 16, Data Listing 17, and Data Listing 18.

11.4.1.1 Primary Endpoint Analysis

The co-primary effectiveness endpoints of the study were the sensitivity and specificity of ^{64}Cu-DOTATATE PET-CT imaging when each imaging reader's subject-level result was compared to a SOT for the subject, with primary endpoint success defined as the same two out of three readers having sensitivity and specificity results exceeding the specified thresholds.

Table 11.4.1.1-1 presents the individual reader results for PET imaging versus SOT. All three readers demonstrated success on the co-primary effectiveness endpoints with Sensitivity >70% and Specificity >60%. All three readers had point estimates of sensitivity of ^{64}Cu-DOTATATE to be >90% for detecting disease when disease was present relative to the SOT. Two of the three readers had point estimates of specificity greater ≥90% while the third had a point estimate of specificity equal to 80% in determining absence of disease when disease was indeed absent. All readers passed the sensitivity and specificity hypotheses testing at a one-sided α=0.025 level of significance.

Table 11.4.1.1-1: Summary of Individual Reader Results for ^{64}Cu-DOTATATE PET Imaging Versus SOT – EE Population (N=63)

Reader	Parameter	Estimate (95% CI)	p-Value	Reader Passes Sensitivity and Specificity Hypotheses?
Reader 1	Sensitivity	0.9091 (0.7643, 0.9686)	0.0042	Yes
	Specificity	0.9655 (0.8282, 0.9939)	<0.0001	Yes
Reader 2	Sensitivity	0.9091 (0.7643, 0.9686)	0.0042	Yes
	Specificity	0.8000 (0.6269, 0.9049)	0.0172	Yes
Reader 3	Sensitivity	0.9091 (0.7643, 0.9686)	0.0042	Yes
	Specificity	0.9000 (0.7438, 0.9654)	0.0003	Yes

Source: Data Table 5
CI=Confidence Interval

11.4.1.2 Secondary Endpoint Analysis

The secondary effectiveness endpoints of the study were the majority of readers sensitivity, specificity, PPV, NPV, and accuracy; individual and majority reader sensitivity and specificity in distinguishing between localized and metastatic disease; and individual reader accuracy, PPV, and NPV.

The two-way table utilized to compute sensitivity, specificity, PPV, NPV, and accuracy for the majority read is provided in Table 11.4.1.2-1. Subject PD-NET3-013 had a Not Evaluable read for Reader 1 (Data Listing 18), and therefore, the total number of images in the two-way table is 1 fewer than the EE population count. Table 11.4.1.2-2 provides the majority read summary statistics for ^{64}Cu-DOTATATE PET imaging versus SOT.

The majority of readers showed statistically significant sensitivity (0.9091, p=0.0042) and specificity (0.9655, p<0.0001) in detecting patients positive for disease and patients negative for disease, respectively. The probability of disease being present given a positive result with ^{64}Cu-DOTATATE (PPV) was 0.9677. The probability of disease being absent given a negative result with ^{64}Cu-DOTATATE (NPV) was 0.9032. In this study, the majority of readers determined that imaging with ^{64}Cu-DOTATATE had an accuracy of 0.9355.

Table 11.4.1.2-1: ^{64}Cu-DOTATATE PET Majority Read Imaging Versus Standard of Truth Two-Way Table – EE Population (N=63)

		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: Data Table 6

Table 11.4.1.2-2: Summary Statistics for ^{64}Cu-DOTATATE Majority Read Imaging Versus Standard of Truth – EE Population (N=63)

	Summary Statistics		
Parameter	**Estimate**	**95% CI**	**p-Value**
Sensitivity[a]	0.9091	(0.7643, 0.9686)	0.0042
Positive Predictive Value	0.9677	(0.8381, 0.9943)	
Specificity[b]	0.9655	(0.8282, 0.9939)	<0.0001
Negative Predictive Value	0.9032	(0.7510, 0.9665)	
Accuracy	0.9355	(0.8455, 0.9746)	

Source: Data Table 6
CI=Confidence Interval
[a] One sided α=0.025 test of H_{a0}:Sens $\leq$0.70 vs. H_{a1}:Sens>0.70
[b] One sided α=0.025 test of H_{b0}:Spec $\leq$0.60 vs. H_{b1}:Spec>0.60

Individual reader summary statistics for ^{64}Cu-DOTATATE PET imaging versus SOT are provided in Table 11.4.1.2-3. All readers demonstrated a level of accuracy ranging from 0.8571 to 0.9355. Readers 1 and 3 were more accurate in determining the presence or absence of disease relative to the SOT than Reader 2.

Table 11.4.1.2-3: Individual Reader Summary Statistics for ^{64}Cu-DOTATATE PET Imaging Versus SOT – EE Population (N=63)

Reader	Parameter		
	PPV	NPV	Accuracy
1	0.9677	0.9032	0.9355
2	0.8333	0.8889	0.8571
2	0.9091	0.9000	0.9048

Source: Data Table 7

Readers who identified an image as positive were asked to further classify the disease as localized or metastatic. Sensitivity and specificity were determined relative to the SOT. The majority of readers determined from ^{64}Cu-DOTATATE imaging findings that 30 patients were positive for disease while the SOT determined 33 patients were positive for disease. Of the 30 patients identified by the readers via ^{64}Cu-DOTATATE PET imaging as positive for disease, 2 patients were determined to have localized disease while 28 were determined to have metastatic disease. Three instances of localized disease detected by the SOT were not detected by the majority read. The majority of readers had a sensitivity of 1.000 and a specificity of 1.000 in determining localized or metastatic disease among patients imaged with ^{64}Cu-DOTATATE and having an image status of positive for disease (Table 11.4.1.2-4). Individual reader classification of localized and metastatic disease is provided in Data Table 8.

Table 11.4.1.2-4: Majority Read Classification of Localized and Metastatic Disease – EE Population (N=63)

Majority of Readers Classification	Standard of Truth		Sensitivity	Specificity
	Localized Disease (N=5)	Metastatic Disease (N=28)		
Localized Disease	2 (40.0%)	0 (0.0%)	1.0000	1.0000
Metastatic Disease	0 (0.0%)	28 (100.0%)		

Source: Data Table 9

11.4.1.3 Tertiary Endpoint Analysis

For each reader pair (Readers 1&2, Readers 1&3, and Readers 2&3) the inter-reader agreement was assessed using a Cohen's Kappa along with a 95% confidence interval on Cohen's Kappa. A Generalized Fleiss Kappa and associated 95% confidence interval were computed to assess overall agreement among the 3 readers. Readers 1&3 were in greatest agreement (Kappa = 0.8710) among the reader pairs. Overall, the 3 readers demonstrated a relatively high degree of agreement (Kappa = 0.7664). Table 11.4.1.3-1 presents a summary of inter-reader agreement for assessment of ^{64}Cu-DOTATATE imaging.

Table 11.4.1.3-1: Summary of Inter-Reader Agreement for Assessment of ^{64}Cu-DOTATATE Imaging – EE Population (N=63).

Reader Pair	n	Kappa (SE)	95% CI on Kappa
1 vs. 2	62	0.7419 (0.0844)	(0.5764, 0.9074)
1 vs. 3	62	0.8710 (0.0623)	(0.7489, 0.9930)
2 vs. 3	63	0.7123 (0.0883)	(0.5392, 0.8855)
Overall	63	0.7664 (0.0732)	(0.6229, 0.9099)

Source: Data Table 11
SE=Standard Error
CI=Confidence Interval

Intra-reader variability was assessed using n=7 randomly chosen study images that were re-read by the readers. Cohen's Kappa was computed for each reader on the pairs of re-reads for each image. A 95% confidence interval on Cohen's Kappa was computed. A generalized Kappa and 95% confidence interval were computed in order to assess overall intra-reader reliability. Readers 1 and 3 demonstrated perfect intra-reader agreement upon image re-read. Table 11.4.1.3-2 presents a summary of intra-reader agreement of ^{64}Cu-DOTATATE PET imaging.

Table 11.4.1.3-2: Summary of Intra-Reader Agreement of ^{64}Cu-DOTATATE PET Imaging – EE Population (N=63)

		Summary Statistics	
Reader	**Parameter**	**Estimate**	**95% CI**
1	Kappa	1.0000	(1.0000, 1.0000)
	Uncorrected Agreement	1.0000	(0.5904, 1.0000)
2	Kappa	0.5333	(0.0596, 1.0000)
	Uncorrected Agreement	0.7143	(0.2904, 0.9633)
3	Kappa	1.0000	(1.0000, 1.0000)
	Uncorrected Agreement	1.0000	(0.5904, 1.0000)

Source: Data Table 10
CI=Confidence Interval

11.4.1.4 Pharmacokinetic Analysis

The results of the PK assessment are presented in Section 16.1.11.

11.4.2 Statistical and Analytical Summary

11.4.2.1 Adjustments for Covariates

Not applicable.

11.4.2.2 Handling of Dropouts or Missing Data

In the statistical analysis of the primary effectiveness endpoints of the study, only subjects with evaluable endpoints were used in the statistical analyses (i.e., a complete case analysis).

11.4.2.3 Interim Analysis and Data Monitoring

No interim analysis was planned or performed for this study.

11.4.2.4 Use of an "Efficacy Subject" of Subjects

Not applicable.

11.4.2.5 Examination of Subgroups

No subgroup analyses were planned or performed.

11.4.3 Drug Dose, Drug Concentration, and Relationship to Response

All subjects in this study received the same intended dose of ^{64}Cu-DOTATATE. Therefore, no drug-dose or drug-concentration response was expected.

11.4.4 Drug-Drug and Drug-Disease Interactions

There do not appear to be any drug-drug or drug-disease interactions related to the use of ^{64}Cu-DOTATATE in this study.

11.4.5 By-Subject Displays

Not applicable.

11.4.6 Efficacy Conclusions

- A total of 68 subjects were screened for this study. Of these, 66 were enrolled and 63 (95.5%) completed the study. Three subjects (4.5%) withdrew consent. A total of 63 subjects were injected with a mean dose of 4.11 mCi of ^{64}Cu-DOTATATE.
- Based on the individual reader analysis, all three readers demonstrated success on the co-primary effectiveness endpoints with Sensitivity >70% and Specificity >60%.
- The majority read analysis showed statistically significant sensitivity (0.9091, $p=0.0042$) and specificity (0.9655, $p<0.0001$) in detecting patients positive for disease and patients negative for disease, respectively. The probability of disease being present given a positive result with ^{64}Cu-DOTATATE (PPV) was 0.9677. The probability of disease being absent given a negative result with ^{64}Cu-DOTATATE (NPV) was 0.9032. In this study, the majority read analysis determined that imaging with ^{64}Cu-DOTATATE had an accuracy of 0.9355.
- The majority read analysis had a sensitivity of 1.000 and a specificity of 1.000 in distinguishing between localized or metastatic disease among patients imaged with ^{64}Cu-DOTATATE and having an image status of positive for disease.
- All readers demonstrated a level of accuracy ranging from 0.8571 to 0.9355. Readers 1 and 3 were more accurate in determining the presence or absence of disease relative to the SOT

than Reader 2. Reader 1 had a PPV of 0.9677, NPV of 0.9032, and accuracy of 0.9355; Reader 2 had a PPV of 0.8333, NPV of 0.8889, and accuracy of 0.8571; and Reader 3 had a PPV of 0.9091, NPV of 0.9000, and accuracy of 0.9048.

- Overall, the 3 readers demonstrated a high degree of inter-reader agreement (Kappa = 0.7664).
- Relative to the 7 images that were re-read, Readers 1 and 3 demonstrated perfect intra-reader agreement upon image re-read (Kappa = 1.000).
- It can be concluded that ^{64}Cu-DOTATATE is an effective imaging agent in detecting the presence or absence of a NET.

12 SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

All 63 subjects were injected with a single dose of ^{64}Cu-DOTATATE. A mean (SD) dose of 4.11 (0.17) mCi of ^{64}Cu-DOTATATE was delivered. Doses ranged from 3.6 mCi to 4.4 mCi. Table 12.1-1 provides a summary of ^{64}Cu-DOTATATE dose administration.

A by-subject listing of drug administration is provided in Data Listing 14 and a by-subject listing of the PET imaging procedure is provided in Data Listing 15.

Table 12.1-1: Summary of ^{64}Cu-DOTATATE Dose Administration

	Mean	SD	n	Min	Max	Median
^{64}Cu-DOTATATE Delivered (mCi)	4.11	0.17	63	3.6	4.4	4.13
Mass dose of 64Cu-DOTATATE Delivered (mcg)	17.48	6.27	63	8.5	38.3	16.10

Source: Data Table 12

12.2 ADVERSE EVENTS

12.2.1 Display of Adverse Events

Overall there were 9 adverse events experienced by 5 subjects. The most common adverse events were gastrointestinal disorders (4.8%), nervous system disorders (3.2%), vascular disorders (3.2%), and skin and subcutaneous tissue disorders (1.6%).

The number and percentage of subjects with adverse events are summarized by preferred term and system organ class in Table 12.2.1-1. Adverse events summarized in this table include all events recorded in the Adverse Events CRF. For a complete list of events and other symptoms recorded in the database see Data Listing 7.

Table 12.2.1-1: Number and Percentage of Subjects with Adverse Events (Safety Population)

Adverse Event Category	Overall (N=63)
Total Number of Adverse Events	9
Subjects with at Least One Adverse Event	5 (7.9%)
Gastrointestinal Disorders	3 (4.8%)
Nausea	1 (1.6%)
Vomiting	2 (3.2%)
Nervous System Disorders	2 (3.2%)
Headache	1 (1.6%)
Syncope	1 (1.6%)
Skin and Subcutaneous Tissue Disorders	1 (1.6%)
Melanoderma	1 (1.6%)
Vascular Disorders	2 (3.2%)
Flushing	1 (1.6%)
Hypertension	1 (1.6%)

Source: Data Table 13

12.2.2 Analysis of Adverse Events

12.2.2.1 Adverse Events by Severity

Adverse events by severity are presented in Data Table 14. A total of 4 subjects (6.3%) experienced 7 adverse events that were mild in severity and 2 subjects (3.2%) experienced 2 adverse events that were moderate in severity. There were no adverse events that were severe, life-threatening or disabling, or that resulted in death. Adverse events that were mild in severity included nausea, vomiting, headache, melanoderma, and flushing. Adverse events that were moderate in severity included syncope and hypertension.

12.2.2.2 Adverse Events by Relationship

Adverse events by relationship to treatment are presented in Data Table 15. A total of 5 subjects (7.9%) experienced 8 adverse events that were determined to be probably not related to treatment with ^{64}Cu-DOTATATE. These adverse events included nausea, vomiting, headache, syncope, melanoderma, and flushing. One subject (1.6%) experienced an adverse event of hypertension that was determined to be definitely not related to treatment with ^{64}Cu-DOTATATE.

12.2.3 Listing of Adverse Events by Subject

A by-subject data listing of all AEs for the safety population is provided in Data Listing 7.

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

No deaths, other serious adverse events, or other significant adverse events occurred during the course of this study.

12.4 CLINICAL LABORATORY EVALUATIONS

There were no clinically significant changes from baseline in mean serum chemistry or hematology values that occurred post-injection with ^{64}Cu-DOTATATE or at the Day 1-2 follow-up visit. Of note, shift tables for creatinine presented a shift from a normal value at baseline to a high value at the Day 1-2 visit in 6 subjects (9.5%) (Data Table 30). Shift tables for glucose presented a shift from a normal value at baseline to a high value post-injection in 5 subjects (7.9%) and a shift from a normal value at baseline to a high value at the Day 1-2 visit in 13 subjects (20.6%) (Data Table 31). Shift tables for sodium presented a shift from a normal value pre-injection to a low value post-injection in 9 subjects (14.3%) which had resolved by the Day 1-2 visit (Data Table 34).

A by-subject listing of serum chemistry and hematology laboratory profiles are provided in Data Listing 9 and Data Listing 10, respectively.

12.5 VITAL SIGNS, PHYSICAL EXAMINATIONS, AND OTHER OBSERVATIONS RELATED TO SAFETY

12.5.1 Vital Signs

There were no clinically significant changes from baseline in mean vital signs occurring at 5-, 10-, 30-, or 60- minutes post-injection or at discharge. Mean systolic blood pressure was elevated at all time points from pre-injection to discharge and fluctuated from a mean low of 130.48 mmHg pre-injection to a mean high of 137.10 mmHg at 60 minutes post-injection. Upon discharge, the mean systolic blood pressure was 132.97 mmHg.

A by-subject listing of vital signs is provided in Data Listing 8.

12.5.2 Physical Examinations

All physical exam findings were normal with the exception of 2 subjects. Subject GG-NET3-023 had mild high blood pressure at screening and subject MS-NET3-044 had controlled hypertension at screening.

A by-subject listing of physical exam findings is provided in Data Listing 13.

12.5.3 ECG Parameters

There were no shifts observed in ECG parameters from baseline to 1 hour post-injection of ^{64}Cu-DOTATATE.

A summary of ECG shift is provided in Data Table 18.

12.5.4 Concomitant Medications

A by-subject listing of concomitant medications is provided in Data Listing 11.

12.6 SAFETY CONCLUSIONS

The following conclusions can be drawn from the safety analyses:

- Overall there were 9 adverse events experienced by 5 subjects. The most common adverse events by MedDRA system organ class were gastrointestinal disorders (4.8%), nervous system disorders (3.2%), vascular disorders (3.2%), and skin and subcutaneous disorders (1.6%).
- All adverse events were either mild or moderate in severity. There were no adverse events that were severe, life-threatening or disabling, or that resulted in death. Adverse events that were mild in severity included nausea, vomiting, headache, melanoderma, and flushing. Adverse events that were moderate in severity included syncope and hypertension.
- All adverse events were either probably not related or definitely not related to injection of a single dose of ^{64}Cu-DOTATATE. No adverse events were considered definitely related, probably related, or possibly related to ^{64}Cu-DOTATATE injection.
- There were no serious adverse events reported in subjects injected with ^{64}Cu-DOTATATE.
- There were no clinically significant changes from baseline in mean serum chemistry or hematology values that occurred post-injection with ^{64}Cu-DOTATATE or at the Day 1-2 follow-up visit.
- There were no clinically significant changes from baseline in mean vital signs occurring at 5-, 10-, 30-, or 60- minutes post-injection or at discharge.
- There were no shifts observed in ECG parameters from baseline to 1 hour post-injection of ^{64}Cu-DOTATATE.
- Injection of a single dose of ^{64}Cu-DOTATATE appears to be safe and well tolerated in this patient population.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 DISCUSSION

The primary objective of this study was to assess the performance (sensitivity and specificity) of ^{64}Cu-DOTATATE PET-CT imaging in subjects with known or suspected NETs, when comparing individual reader results to a standard of truth for each subject. Success was defined as the same two out of three readers having sensitivity and specificity results exceeding the specified thresholds. All three readers demonstrated success on the co-primary effectiveness endpoints with individual sensitivity >70% and individual specificity >60%.

Additionally, the study sought to characterize the predictive value of ^{64}Cu-DOTATATE PET-CT imaging when comparing an imaging reader-majority rule determination to the SOT for each subject and also when the comparison was performed on an individual reader basis. The majority of readers showed statistically significant sensitivity (0.9091, p=0.0042) and specificity (0.9655, p<0.0001) in detecting patients positive for disease and patients negative for disease, respectively. The probability of disease being present given a positive result with ^{64}Cu-DOTATATE (PPV) was 0.9677. The probability of disease being absent given a negative result with ^{64}Cu-DOTATATE (NPV) was 0.9032. In this study, the majority of readers determined that imaging with ^{64}Cu-DOTATATE had an accuracy of 0.9355.

In evaluating the imaging performance (sensitivity and specificity) of ^{64}Cu-DOTATATE when comparing an imaging reader-majority rule determination to the SOT for each subject the majority of readers had a sensitivity of 1.000 and a specificity of 1.000 in determining localized or metastatic disease. Overall, the readers demonstrated a level of accuracy ranging from 0.8571 to 0.9355.

Furthermore, intra-reader and inter-reader agreement were evaluated. Overall, the three readers demonstrated a relatively high degree of inter-reader agreement (Kappa=0.7664). Readers 1 and 3 demonstrated perfect intra-reader agreement (Kappa=1.0000).

It is important to note that failures in detecting disease were retrospectively reviewed by the investigators after the database was locked. Upon review of these failures it was noted that three SOT image reads determined to be positive for disease by the oncologist were in fact negative for disease. Included in these miscalls were subjects 42, 43, and 51. Each of these subjects had their primary tumor resected prior to determining the SOT and as such should have had a SOT negative for disease. The oncologists have included a note-to-file, provided in Section 16.1.12, describing this error. Taking this into account Readers 1 & 3 and the Majority Read would have a sensitivity of 1.000, a specificity of 0.9688, PPV of 0.9677. NPV of 1.000, and accuracy of 0.9839. Reader 2 would have a sensitivity of 1.000, specificity of 0.8182, PPV of 0.8333, NPV of 1.000, and accuracy of 0.9048.

The safety of ^{64}Cu-DOTATATE was measured by evaluating adverse events, vital signs, clinical laboratory parameters, and ECG recordings. There were 9 reported adverse events experienced by 5 subjects of which all were mild to moderate in severity and none were related to injection of ^{64}Cu-DOTATATE. There were no adverse events that were severe, life-threatening or disabling, or that resulted in death. Additionally, no serious adverse events were reported during the course of this study. There were no clinically significant changes from baseline in mean serum chemistry or hematology values that occurred post-injection of ^{64}Cu-DOTATATE or at the Day 1-2 follow-up visit nor were there clinically significant changes from baseline in mean vital signs

at 5-, 10-, 30-, or 60- minutes post-injection or at discharge. Furthermore, there were no observed shifts in ECG parameters from baseline to 1-hour post-injection of ^{64}Cu-DOTATATE.

Safety data from this study are consistent with safety data reported from the two prior clinical studies of ^{64}Cu-DOTATATE. Subjects in the retrospective study were observed for adverse events. Upon conclusion of that study there were no adverse events or clinically detectable pharmacologic effects observed. Adverse events, vital signs, clinical laboratory parameters, and ECG recordings were collected in the dose ranging study. At the conclusion of that study there were no adverse events related to treatment with ^{64}Cu-DOTATATE nor were there any safety concerns based upon ECG parameters, vital signs, or clinical laboratory values.

This study demonstrates that ^{64}Cu-DOTATATE appears to be an effective agent in detecting the presence or absence of a NET as well as for distinguishing between localized and metastatic disease. Injection of a single dose of ^{64}Cu-DOTATATE appears to be safe and was well tolerated by study subjects.

13.2 CONCLUSIONS

The following conclusions were elicited from the results of this study:

- ^{64}Cu-DOTATATE has both a high sensitivity and specificity in detecting patients with and without NETs, respectively.
- ^{64}Cu-DOTATATE has a high sensitivity and specificity in determining localized or metastatic disease.
- ^{64}Cu-DOTATATE PET-CT image reads have a high level of inter-reader and intra-reader agreement.
- Imaging with ^{64}Cu-DOTATATE appears to be safe, effective, and well tolerated.

14 TABLES AND FIGURES NOT INCLUDED IN THE TEXT (SOME REFERRED AS SOURCE)

15 REFERENCE LIST

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16 APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol

The final protocol dated 15 October 2018 reflecting 2 amendments is attached.

Original

The original protocol was dated 05 June 2018, and was amended on the following dates:

Amendments

- Amendment 1: 05 October 2018
- Amendment 2: 15 October 2018

16.1.2 Sample Case Report Forms (CRFs)

A blank casebook of CRFs is attached.

16.1.3 Institutional Review Board and Subject Consent and Information

16.1.3.1 Name and Address of Institutional Review Board

Biomedical Research Alliance of New York
1981 Marcus Avenue, Suite 210
Lake Success, New York 11042

16.1.3.2 Sample Informed Consent Form (ICF)

The sample ICF approved by the IRB is attached.

16.1.4 Description of Investigators, Investigator CVs, and FDA 1572

16.1.4.1 Investigators and Locations

Principal Investigator and location for this study were as follows, for the 1 active site:

Excel Diagnostics and Nuclear Oncology Center
Principal Investigator: Rodolfo Nunez, M.D.
9701 Richmond Ave.
Houston, TX 77042

16.1.4.2 Curriculum Vitae of Principal Investigators and FDA 1572

Curriculum vitae and FDA 1572 from the principal investigator named in Appendix 16.1.4.1 are attached.

16.1.5 Signature of Sponsor's Responsible Officer or Medical Representative

FINAL APPROVAL

To the best of my knowledge, this clinical study report accurately describes the conduct and the results of this clinical study.

David Ranganathan, PhD
Senior Scientist
RadioMedix, Inc.

Signature _____ Date _____

Ebrahim S. Delpassand, MD, FACNM
Chairman and CEO
RadioMedix, Inc.

Signature _____ Date _____

16.1.6 Listing of Patients Receiving Test Drug(s)/Investigational Product(s) from Specific Batches, Where More Than One Batch Was Used

A listing of batch numbers is attached.

16.1.7 Subject Randomization Scheme and Codes

Not applicable.

16.1.8 Audit Certificates (if available)

Not applicable.

16.1.9 Documentation of Statistical Methods

The final SAP (Version 1.1; 07 November 2018) is attached.

16.1.10 Documentation of Inter laboratory Standardization Methods and Quality Assurance Procedures, if Used

Documentation of laboratory QA methods is attached.

16.1.11 Pharmacokinetic Assessment Report

The PK Assessment Report is attached.

16.1.12 Oncologist Note to File

The Oncologist Note to File discussed in Section 13.1 is attached.

16.1.13 Clinical Laboratory and PET Imaging Deviations

The listing of PET-CT image acquisition deviations is attached.

The listing of clinical laboratory deviations is attached.

16.1.14 Publications Based on the Study

Not applicable.

16.1.15 Important Publications Referenced in the Report

Important publications referenced in the report are attached via the links in Section 15.

16.2 SUBJECT DATA LISTINGS

Listing 1	Subject Completion/Withdrawal
Listing 2	Inclusion Criteria Violations
Listing 3	Exclusion Criteria Violations
Listing 4	Subjects Excluded from Safety Population
Listing 5	Subjects Excluded from EE Population
Listing 6	Demographics
Listing 7	Adverse Events
Listing 8	Vital Signs
Listing 9	Subject Laboratory Profiles – Serum Chemistry
Listing 10	Subject Laboratory Profiles – Hematology
Listing 11	Concomitant Medications
Listing 12	Medical History
Listing 13	Physical Exam
Listing 14	Drug Administration
Listing 15	PET Imaging Procedure
Listing 16	Standard of Truth Data Listing
Listing 17	Central Radiology Data Listing
Listing 18	Efficacy Data Listing

16.3 CASE REPORT FORMS

Completed CRFs for all screened subjects are attached.

16.4 INDIVIDUAL SUBJECT DATA LISTINGS

Individual subject data listings were not generated for this study. Subject-level data are presented in the subject data listings in Section 16.2 and contained in the final study database.