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

Statistical Methods:

Analysis Populations

The following analysis populations were defined:

Efficacy Evaluable (EE) Population – The EE population consisted of all subjects who were enrolled in the study (plus 4 subjects from the selected dose cohort of the Phase 1 study having the same radiation dose (4.0 mCi) as used in this study), 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.

General Statistical Methodology

A table was constructed with counts and percentages of the number of subjects who were screen failures, the number of subjects enrolled in the study, the number of subjects withdrawn from the study before study completion, and the number who completed the study. For those subjects who withdrew before completion of the study, counts and percentages of the reasons for withdrawal were tabulated.

The continuous demographic characteristics at screening 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 were summarized for the safety population using frequency counts and percentages.

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

In order to have at least an 80% probability of showing that the sensitivity was at least 70% and the specificity was at least 60% a sample of $n_1 = 42$ positive subjects and $n_2 = 21$ negative subjects was necessary. This sample size was derived under the assumptions that (1) the readers were reading the same images and that their reads were correlated at r = 0.70; (2) exact binomial tests were used with an alpha level of 0.025 for the hypotheses

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

and

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

(3) the actual sensitivity was 0.90; and, (4) the actual specificity was 0.90. In order to assure a power of at least 0.80 for two tests together, the individual tests were powered at 0.90.

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

Primary Efficacy Analysis

The EE population was the primary analysis set for all effectiveness analyses. The co-primary effectiveness endpoints were computed as follows:

sensitivity = (# true positive)/(# true positive + # false negative)

specificity = (# true negative)/(# true negative + # false positive)

Each hypothesis test was conducted at the one-sided $\alpha = 0.025$ level of significance. Point estimates of sensitivity and specificity were calculated with a 95% confidence limits. Confidence limits for all binomial parameters (sensitivity, specificity, PPV, NPV and accuracy) were calculated using Wilson's score method with continuity correction (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 must have achieved success upon sensitivity and specificity.

Safety Analysis

The safety population was used for the analysis of all safety variables and baseline characteristics. Prior to analysis, all AEs were coded using the MedDRA coding dictionary. Based on these coded terms, TEAEs were summarized using system organ class and preferred terms, as well as by relationship to ^{64}Cu-DOTATATE. All AEs were listed, regardless of whether or not they were study treatment related.

Vital signs were summarized using descriptive statistics (mean, standard deviation, median, minimum, maximum, and number of non-missing observations) by time point. Changes from baseline were also summarized by post-dose time point.

Clinical laboratory parameters were summarized using descriptive statistics (mean, standard deviation, median, minimum, maximum, and number of non-missing observations) by time point. Changes from baseline were also summarized by post-dose time point. In addition, a shift table was constructed to show the shifts in laboratory results by parameter relative to the normal ranges. The number and percentage of subjects with the following shifts was presented: normal/normal, normal/low, normal/high, low/low, low/normal, low/high, high/low, high/normal, and high/high.

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.

Pharmacokinetic Analysis

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

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.