Targeted alpha-emitter therapy of neuroendocrine tumors using $^{212}$Pb-octreotate (AlphaMedix™)

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Disclosures

• CEO of RadioMedix Inc.

• Chairman & Medical Director of Excel Diagnostics & Nuclear Oncology Center

• Speaker Bureau of Bayer, Advanced Accelerated Applications (Novartis)

• Consultant ITG GmbH, Endocyte
# Product pipeline for NETs

**AlphaMedix™** 212Pb-labeled octreotate analog

<table>
<thead>
<tr>
<th>Agent/s</th>
<th>Therapeutic area</th>
<th>Discovery</th>
<th>Preclinical Validation</th>
<th>Pharm/Tox</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Approved</th>
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<tbody>
<tr>
<td>NETMedix™</td>
<td>Neuroendocrine Tumors</td>
<td><strong>RMX Curium</strong></td>
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<td>AminoMedix</td>
<td>Kidney protection during PRRT</td>
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<tr>
<td>AlphaMedix™</td>
<td>Neuroendocrine Tumors</td>
<td><strong>RMX Orano Med</strong></td>
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Pb$^{212}$ - In vivo GENERATION OF ALPHA-PARTICLES

- $^{212}$Pb (10.6 h half life) decays to $^{212}$Bi via $\beta$ emission.
- $^{212}$Bi ($t_{1/2}$=60-min) - two decay routes
  - via $\alpha$ emission to $^{208}$Tl
  - via $\beta$ emission to $^{212}$Po
- Both $^{208}$Tl (via $\beta$-emission) and $^{212}$Po (via $\alpha$ emission) decay to stable $^{208}$Pb
- Gamma ray cumulative energy (238.6 keV) with a 43% yield exploited for imaging.
Efficacy studies of AlphaMedix™
Safety, distribution, PK and dosimetry of $^{203}$Pb-octreotate analog (IND # 130960)

Sponsor: RadioMedix Inc.
Study site: Excel Diagnostics and Nuclear Oncology Center
Collaborator: Orano Med

COMPLETED Q1 2017
IND # 130960  $^{203}$Pb-DOTAMTATE

$^{68}$Ga-DOTATATE PET/CT

$^{203}$Pb-AR-RMX SPECT/CT 4h (coronal)

$^{203}$Pb-AR-RMX SPECT
Safety evaluation

• All patients were evaluated and followed up for any evidence of renal, hepatic or hematologic toxicity using NCI common toxicities criteria Version 4.1 up to a month after the radiopharmaceutical injection.

• No significant acute toxicity was observed immediately following scan; no patients required supportive treatment during or after the scans.

• Clinically non-significant transient lymphocytopenia recorded in 5 of 6 patients 24 or 48 hr p.i.; no intervention was required; CBC returned to the baseline.

Comparison of $^{68}$Ga-DOTATATE PET/CT and $^{203}$Pb-AR-RMX SPECT/CT scans

• Independent reads by two NP blinded to the results of the other study.

• $^{68}$Ga-DOTATATE PET/CT scan: total number of 177 lesions detected in 6 patients.

• $^{203}$Pb-Ar-RMX SPECT/CT: 109 lesions.

• Very close correlation (with correlation coefficient of 0.89) between lesions detected by these two modalities.
AlphaMedix™  IND # 133661  $^{212}$Pb-AlphaMedix™

A Phase 1, Non-Randomized, Open-Label, Dose Escalation Study to Determine the Safety and Bio-distribution and preliminary effectiveness of AlphaMedix™ in adult subjects with somatostatin receptor expressing neuroendocrine tumors (NET)

Sponsor: RadioMedix Inc.
Collaborator: ORANO Med LLC.
Study site: Excel Diagnostics and Nuclear Oncology Center
Initiated Q1 2018
Study Objectives

Primary Objective

• Assessment the safety, and dose limiting toxicity (DLT) of ascending doses of AlphaMedix™

Secondary Objective

• Determine the PK, and dosimetry of AlphaMedix™, and the preliminary effectiveness of ascending doses of AlphaMedix™

Study design

Selection of Dose ranging based on results

• pre-clinical toxicity and dosimetry using $^{212}\text{Pb}$-AlphaMedix in animal models

• eIND clinical studies and dosimetry of $^{203}\text{Pb}$-labeled surrogate
Dose Escalation Scheme

- The dose escalation scheme: conventional 3+3 Phase I design.
- 3 patients enrolled in each cohort.
- In the event of a DLT, the cohort will expand to 6 subjects (3+3). If no additional subjects exhibit DLT, dose escalation will continue.
- Study started with SAD (single ascending dose) and switched to the MAD (multi-ascending dose) regimen upon initial clinical improvement and recommendation and the approval of DSMB.
### Inclusion Criteria:

- Signed ICF
- Subjects of either sex, aged ≥18 years
- ECOG status 0-2
- Life expectancy of at least 12 weeks
- All FDA-approved therapies for which the subject is eligible have been exhausted, except PRRT.
- Histologically confirmed diagnosis of SSTR(+) NET, unresectable or metastatic
- Measurable disease per RECIST 1.1 on CT/MRI scans
- CT, MRI, \(^{18}\text{F-FDG PET/CT}, \, ^{68}\text{Ga-Netspot, NAF PET/CT bone scan, ultrasound, etc. of the tumor region or suspected area within the 4 weeks of dosing day\)
Tumor Characterization and Staging

- Somatostatin receptor imaging (SRI)
- Histopathology
- Morphological and functional imaging
  - MRI or CT of chest, abdomen and pelvis with contrast agent
  - $^{18}$F-FDG PET-CT to monitor response and to switch from SAD to MAD (if baseline positive)
  - $^{68}$Ga-DOTATATE PET/CT
- Tumor markers - MAD only part of the study, CgA (baseline, and then every 8 (+/-1) weeks).
- Serotonin, gastrin, insulin, pancreatic polypeptide if elevated at baseline.
- NETEST is added in MAD 4
- Post-therapy imaging SPECT/CT imaging (dosimetry)
- Blood samples (blood chemistry and hematology, PK)
- Glomerular filtration rate ($^{99m}$Tc-DTPA renal scan with GFR determination) at screening and then 8 (+/-1 week).
Efficacy assessment

Imaging response:

• Partial or complete response on CT and/or MRI using RECIST 1.1
• $^{18}$F-FDG PET/CT: complete resolution of metabolic activity if tumor was FDG-avid at baseline.
• The imaging for efficacy performed at 8 (+/-1 week) after the administration of the investigational drug during SAD dosing, and 8 (+/-1 week) after each dose during MAD dosing.
Safety assessment

Monitoring kidneys, liver, and bone marrow function

a) Chemistry: CMP and eGFR

b) Hematology: CBC with differential

c) 12-lead static ECG at screening (if necessary to rule out CHD), before injection and after completion of AA infusion.

Dosimetry

In six subjects starting with the 4th cohort of SAD or after switching to the MAD phase of the study, whichever comes first.
Enrollment

- Scheduled enrollment: maximum of 50 subjects.
- 10 subjects screened, enrolled, and received the investigational agent (as of Jan 2019).
- 1 subject from cohort 3 withdrew consent after 2 cycles and was replaced.

Dosing

- SAD1 and SAD2 completed.
- Cohort 3 was converted from a SAD to MAD3 -three cycle dosing completed,
- Enrolling for MAD 4 in April 2019.

Demographics

<table>
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<tr>
<th>Parameter</th>
<th>SAD1 (n=3)</th>
<th>SAD2 (n=3)</th>
<th>MAD3 (n=4)</th>
<th>Overall (n=10)</th>
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<tbody>
<tr>
<td>Age (range)</td>
<td>75 - 77</td>
<td>27 - 72</td>
<td>61 - 68</td>
<td>27 - 77</td>
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<td>2</td>
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</table>
Pharmacokinetics studies: Blood clearance

PK results of AlphaMedix (%ID) in the MAD 3 cohort

%ID in the total blood

Time since administration in hours
Evaluation of renal, hepatic and bone marrow toxicity

NCI common toxicity criteria: renal, hepatic, hematological or bone marrow toxicity.

- The treatment well tolerated with no DLTs in any cohort.
- No significant acute toxicity observed

- No patients required supportive care during therapy
- Grade 1 bone marrow toxicity: 5 out 10 patients
- Grade 4 lymphopenia: in cohort 3 after 3 cycles (when Grade 2 at baseline)
- Grade 1 hepatic toxicity: 3 out of 10 patients (cohort 3)
- Follow up studies: no cardiac toxicity (ECG), or decrease in kidney function (GFR)
- Moderate or severe nausea/vomiting: 3 out of 10 patients (recovered within 1 day)
- Transient hair loss: 3 out of 10 patients
- Energy level and appetite improvement (3 doses): 2 out of 3 patients in MAD3
Preliminary evaluation of the efficacy

**AlphaMedix™ cohort 3-03 (3rd cycle) SPECT/CT**

- Stable disease in all subjects per RECIST 1.1.
- Decrease in max SUV by PET scans (\(^{18}\)FDG and/or \(^{68}\)Ga-DOTATATE) after 2 cycles in 2 patients MAD3.
Summary:

AlphaMedix is the first TAT agent for metastatic SSTR expressing NET undergoing clinical trial under FDA proceed authorization, in U.S.

²¹²Pb isotope sufficient amount available to support commercial scale up.

DMF filled (2017-ORANO Med)

Completed dosing of SAD1 and SAD2 dose escalation cohort and first MAD cohort

The treatment well tolerated with no clinically significant DLTs in any cohort.

Stable disease in all subjects per RECIST 1.1.
<table>
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<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>January 2017</td>
<td>PCT application (priority date)</td>
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<tr>
<td>December 2018</td>
<td>SBIR phase I &amp; Trademark AlphaMedix™</td>
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<tr>
<td>January, 2018</td>
<td>FDA approval for initiation of Phase I clinical trial of AlphaMedix™</td>
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<tr>
<td>February, 2018</td>
<td>First AlphaMedix™ patient injected</td>
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<tr>
<td>July 2018</td>
<td>First MAD cohort of AlphaMedix initiated</td>
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<tr>
<td>August 2018</td>
<td>ODD application submitted (granted Oct 18)</td>
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<td>November 2018</td>
<td>NIH NCI Phase II Contract - $2M</td>
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<tr>
<td>Q1 2020</td>
<td>Completion of dose escalation trial</td>
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<td>Preparation for meeting with FDA and design of the phase II/III</td>
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THANK YOU!