Patient-Specific Cellular Therapy (Ixmyelocel-T) is Safe and Improves Time to Treatment Failure in Patients with Critical Limb Ischemia and No Revascularization Options

American Heart Assoc Scientific Sessions 2011

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For the RESTORE-CLI Clinical Investigators
Orlando, FL
November 14, 2011
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FINANCIAL DISCLOSURE:
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Ixmyelocel-T: Description

• Autologous (patient-specific), expanded multicellular therapy
• Target population: CLI patients with no options for revascularization
• Cell source: Bone marrow
• Cell delivery: Twenty intramuscular injections in lower extremity
Ixmyelocel-T Production

**Day 1**
- Bone marrow (approx. 50ml / 3 tablespoons) is taken from patient’s hip
- 15 minute outpatient procedure

**Days 2-13**
- Automated system expands key beneficial cell types

**Day 14**
- Expanded multicellular therapy is administered to the same patient
- 20 minute in-office procedure for CLI patients
Ixmyelocel-T Cell Expansion

Starting Bone Marrow

- RBCs
- Lymphocytes (T + B)
- Granulocytes
- Monocytes
- Mesenchymal Stem Cells

Expansion Process

- RBC extraction ≤ 0.1% remaining
- Cell Reduction -5X
- Cell Amplification +200X
- +50X

ixmyelocel-T

~300 million cells

Therapeutic Effect

- Remodelling of ischemic tissue
- Modulation of inflammation
- Promotion of angiogenesis

~150 million cells
Ixmyelocel-T Has Multiple Biological Activities

- Remodeling of tissues
  - Secretion of MMPs
  - Phagocytosis and efferocytosis
  - Contraction of ECM
- Promotion of angiogenesis
  - Secretion of angiogenic cytokines
  - Activation of eNOS
- Resolution of inflammation
  - Secretion of anti-inflammatory cytokines
  - Alternatively activated macrophages
Phase 2b RESTORE-CLI Study Design

• Randomized, placebo controlled
• Double-blind
• Powered as Phase 2 safety study
• 150 patients
• 18 active centers
• No-option CLI patients who had rest pain with or without baseline wounds
Key Inclusion Criteria

• Age 18-90
• Diagnosed CLI
  – Ischemic rest pain $\geq$ 2 weeks duration
  – Ulceration or gangrene of toe or foot
  – Toe systolic pressure $\leq$ 50 mmHg
  – Ankle systolic pressure $\leq$ 70 mmHg
• Infrainguinal occlusive arterial disease judged not amenable to revascularization
Key Exclusion Criteria

- Previous amputation at talus or above
- Failed ipsilateral revascularization within 2 weeks of randomization
- Active infection of target extremity
- HbA1c > 10%
- Untreated aorto-iliac occlusive disease
- Exposed tendon or bone in wound
Study Protocol

- 2:1 randomization
  - ixmyelocel-T
  - placebo injection (acellular vehicle)
- One-time set of 20 intramuscular injections 0.5 ml each
  - Lower thigh
  - Calf
  - Foot
- 12 month follow-up
Defined Study Outcomes

• Safety population: all pts randomized and aspirated
• Efficacy population: all pts randomized, aspirated and treated
• Primary (safety): All adverse events
• Primary efficacy: Time to first occurrence of treatment failure (TTF)
  – Major amputation of treated leg
  – All-cause mortality
  – Doubling of wound total surface area from baseline
  – De novo gangrene
• Secondary: Amputation-free survival (AFS)
  – Major amputation of treated leg
  – All-cause mortality
RESTORE-CLI Results: Patient Flow

- Based on interim analysis, randomization stopped at 86 patients
- 9 withdrew prior to aspiration
- 77 aspirated
- 72 received treatment injections
  - 48 ixmyelocel-T
  - 24 placebo control
### Patient Disposition –
### All Treated Patients (n=72)

<table>
<thead>
<tr>
<th></th>
<th>Ixmyelocel-T N = 48(%)</th>
<th>Control N =24(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed</td>
<td>39 (81)</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Died</td>
<td>3 (6)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Withdrew</td>
<td>6 (13)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>-w/endpoint*</td>
<td>3 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>-w/o endpoint</td>
<td>3 (6)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

* All 3 patients had a major amputation prior to withdrawing from the study.
### Patient Demographics—All Treated Patients (n=72)

<table>
<thead>
<tr>
<th>Parameter* (Mean values)</th>
<th>Ixmyelocel-T N = 48</th>
<th>Control N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Male</td>
<td>71</td>
<td>58</td>
</tr>
<tr>
<td>Age</td>
<td>69</td>
<td>67</td>
</tr>
<tr>
<td>% Current, % Past smokers</td>
<td>17, 67</td>
<td>38, 46</td>
</tr>
<tr>
<td>% Current, % Past alcohol</td>
<td>44, 23</td>
<td>29, 33</td>
</tr>
<tr>
<td>BMI</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Creatinine mg/dL</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>N (%) with known Diabetes</td>
<td>21 (44)</td>
<td>15 (63)</td>
</tr>
</tbody>
</table>

*No significant differences*
Time to First Occurrence of Treatment Failure – All Treated Patients (N=72)

62% risk reduction: HR 0.38, 95%CI = (0.20-0.74)
First Event Contributed to Treatment Failure – All Treated Patients (N=72)

<table>
<thead>
<tr>
<th>Endpoint (n)</th>
<th>Ixmyelocel-T N = 48</th>
<th>Control N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major amputation</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Doubling in total wound surface area*</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>De novo gangrene</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Total n(%)</td>
<td>19 (39.6%)**</td>
<td>16 (66.7%)**</td>
</tr>
</tbody>
</table>

*For wound size doubling: patient must have come into the study with a wound to be eligible to contribute to this event.

** p = 0.0451, Fisher’s exact test.
Amputation-Free Survival – All Treated Patients (N=72)

32% risk reduction: HR 0.68, 95%CI = (0.28-1.65)
Post Hoc Analysis – Patients with Baseline Wounds

• Patients with Baseline Wounds – 45 of 72 treated patients
  – Ixmyelocel-T: 29 / 48 patients (60.4%)
  – Control: 16 / 24 patients (66.7%)

• Repeat analysis for only those patients with baseline wounds
  – TTF
  – AFS
TTF and AFS – Baseline Wound Patients (N=45)

77% risk reduction: HR = 0.225
95% CI = (0.103, 0.490)
Cox PH p-value for treatment = 0.0002

61% risk reduction: HR = 0.391
95% CI = (0.131, 1.164)
Cox PH p-value for treatment = 0.0915
Safety Overview:  
All Aspirated Patients (N=77)

<table>
<thead>
<tr>
<th>Safety Parameter</th>
<th>Ixmyelocel-T N = 53</th>
<th>Control N = 24</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%) with Adverse Events</td>
<td>47 (89)</td>
<td>23 (96)</td>
<td>0.424</td>
</tr>
<tr>
<td>N (%) Serious Adverse Event</td>
<td>23 (43)</td>
<td>12 (50)</td>
<td>0.628</td>
</tr>
<tr>
<td>N (%) withdrawal due to AE</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>N (%) Deaths *</td>
<td>3 (6)</td>
<td>2 (8)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

* An additional ixmyelocel-T patient died ~100 days after completing study.  
** Based on Fisher’s Exact Test.
Safety Overview: AEs in ≥ 10% of Aspirated Patients

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Ixmyelocel-T N = 53</th>
<th>Control N = 24</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain in extremity</td>
<td>17 (32)</td>
<td>4 (17)</td>
<td>0.181</td>
</tr>
<tr>
<td>Gangrene</td>
<td>7 (13)</td>
<td>6 (25)</td>
<td>0.209</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>5 (9)</td>
<td>6 (25)</td>
<td>0.087</td>
</tr>
<tr>
<td>Skin Ulcer</td>
<td>6 (11)</td>
<td>5 (21)</td>
<td>0.303</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (11)</td>
<td>2 (8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (9)</td>
<td>3 (13)</td>
<td>0.699</td>
</tr>
</tbody>
</table>

** Based on Fisher’s Exact Test.
Summary: RESTORE-CLI

- Safety profile for aspiration, injection and treatment with ixmyelocel-T favorable
  - No increased adverse events compared to placebo
- TTF primary endpoint positive
  - Significantly fewer adverse limb events
- 32% reduction in AFS in all treated patients
  - Not significant difference
  - Study not powered for AFS outcome
- Patients with baseline wounds had more pronounced treatment effect
Ixmyelocel-T Development Plan: Phase 3 REVIVE – CLI

- 594 no-option CLI patients with tissue loss followed for 18 months
- Primary Efficacy Endpoint: AFS at 12 months
- 80 sites (site selection ongoing); US only
- 1:1 randomization to ixmyelocel-T or placebo
- Special Protocol Assessment (SPA) concurrence with FDA on trial design, endpoints, and statistical analysis plan
- Screening/enrollment initiation expected 4Q 2011