Intramuscular Administration of Autologous Bone Marrow Cells for Limb Salvage in Critical Limb Ischemia:
Results of the Phase III MOBILE * Trial

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* (MarrOwStim Treatment of LimB Ischemia in Subjects With Severe Peripheral Arterial Disease)
Rationale for MOBILE

Critical Limb Ischemia:
• End stage of peripheral arterial disease
• 53,300 amputations each year

Convincing results from a Phase I trial demonstrating safety and suggesting efficacy of concentrated bone marrow cells in preventing amputation in “no option” CLI


30% CLI patients “No Option for Revascularization”
The MOBILE Trial Design

Inclusion Criteria

- Not a candidate for revascularization.
- Ankle Brachial Index < 0.60, TBI < 0.40
- Rutherford 4 and Rutherford 5 Disease

Exclusion Criteria

- HbA₁C > 10%
- CHF: NYHA Class IV
- Creatinine > 2.5 mg/dl or on Hemodialysis
- Amputation < 30 days from enrollment

Rest Pain

Tissue Loss
The MOBILE Trial Design:
Study Product and Administration

1. Aspirated bone marrow is placed in centrifuge tube.
2. Marrow is concentrated with centrifugation (15 min).
3. Concentrated bone marrow cells are collected.
4. 0.75 cc’s of cBMA is injected IM 1.5 inches deep at 35-40 sites in the index limb.
The MOBILE Trial:
Randomization and Endpoints

• Double-blinded, placebo-controlled trial at 24 centers in the U.S.
• Randomization: 3:1 (cBMA: placebo) ... ethical concerns and enrollment.
• Stratified by Rutherford class and Diabetes

• **Primary Endpoint:**
  **Regulatory:** Amputation Free Survival (AFS) at 52 weeks
  \[AFS = \text{all cause mortality} + \text{amputation}\]

• **Secondary Endpoints:**
  1. **Therapeutic:** Incidence of *major amputation* at 52 weeks
  2. Ankle-Brachial Index, Toe-Brachial Index, Transcutaneous oxygen measurements
  3. 6 minute walk test (6 MWT)
The MOBILE Trial: Results


Screened: 262

Enrolled: 152† (155 limbs)

Randomization

1: placebo n=36

3: cBMA n=119

Placebo  cBMA  P-value

Rutherford

4  19 (52.8%)  65 (54.6%)  .851

5  17 (47.2%)  54 (45.4%)  

Diabetes

No  22 (61.1%)  70 (58.8%)  .849

Yes 14 (38.9%)  49 (41.2%)  

† 80% power to detect 60% reduction of risk for major amputation/death.

The MOBILE Trial: Results
Safety Analysis: no significant differences in SAE or AE between study groups.

<table>
<thead>
<tr>
<th>AE Category</th>
<th>Population (includes long term follow-up as of 6/22/2016)</th>
<th>Placebo (n=36)</th>
<th>cBMA (n=119)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any SAE</td>
<td>25 (69.4%)</td>
<td>70 (58.8%)</td>
<td>.329</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4 (11.1%)</td>
<td>5 (4.2%)</td>
<td>.214</td>
<td></td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>4 (11.1%)</td>
<td>2 (1.7%)</td>
<td>.026*</td>
<td></td>
</tr>
<tr>
<td><strong>AE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>35 (97.2%)</td>
<td>117 (98.3%)</td>
<td>.550</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>4 (11.1%)</td>
<td>2 (1.7%)</td>
<td>.026*</td>
<td></td>
</tr>
<tr>
<td>Low RBC Related Level†</td>
<td>13 (36.1%)</td>
<td>82 (68.9%)</td>
<td>&lt;.001*</td>
<td></td>
</tr>
</tbody>
</table>

† No negative sequelae reported – Lower RBC related level expected with large volume bone marrow aspiration.
## Results:

### Death Plus Amputation (AFS) – All Randomized Subjects (N=155)*

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=36)</th>
<th>cBMA (N=119)</th>
<th>P-value</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with Events (%)</td>
<td>11 (30.56%)</td>
<td>24 (20.17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td></td>
<td></td>
<td>.224</td>
<td>0.64 (0.31 – 1.31)</td>
</tr>
</tbody>
</table>

### Major Amputation – All Randomized Subjects (N=155)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=36)</th>
<th>cBMA (N=119)</th>
<th>P-value</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with Events (%)</td>
<td>8 (22.22%)</td>
<td>19 (15.97%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td></td>
<td></td>
<td>.392</td>
<td>0.70 (0.30 - 1.59)</td>
</tr>
</tbody>
</table>
### Major Amputation: Rutherford 4 (N=84) [Rest Pain]

<table>
<thead>
<tr>
<th>Subjects with Events (%)</th>
<th>Placebo (N=19)</th>
<th>cBMA (N=65)</th>
<th>P-Value</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 (26.32%)</td>
<td>5 (7.69%)</td>
<td>.041*</td>
<td>0.27 (0.08 - 0.95)</td>
</tr>
</tbody>
</table>

#### Survival Analysis

- **Control (N=19)**: 92.3%
- **MarrowStim (N=65)**: 73.7%

**Hazard Ratio (95% CI) = 0.27 (0.08 - 0.95)**

**p-value = .041**
**Major Amputation: Rutherford 5 (N=71) [Tissue Loss]**

<table>
<thead>
<tr>
<th>Subjects with Events (%)</th>
<th>Placebo (N=17)</th>
<th>cBMA (N=54)</th>
<th>P-Value</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 (17.65%)</td>
<td>14 (25.93%)</td>
<td></td>
<td>.548*</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td></td>
<td></td>
<td>1.46 (0.42 - 5.10)</td>
<td>82.4%</td>
</tr>
</tbody>
</table>

![Graph showing survival rates and hazard ratio](image)

- **Survival**
  - Control (N=17)
  - MarrowStim (N=54)

- **Hazard Ratio (CI) = 1.46 (0.42 - 5.10)**
- **p-value = .548**
- **82.4%**
- **74.1%**
### Major Amputation: Non-Diabetic (N=92)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=22)</th>
<th>cBMA (N=70)</th>
<th>P-Value</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with Events (%)</td>
<td>6 (27.27%)</td>
<td>7 (10.00%)</td>
<td>.046*</td>
<td>0.33 (0.11 - 0.98)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Graph:**
- **Control (N=22):**
  - Survival: 90.0%
- **MarrowStim (N=70):**
  - Survival: 72.7%

**Hazard Ratio (CI):** 0.33 (0.11 - 0.98)  
**p-value:** .046*  
**Censored:**
Major Amputation: Diabetic (N=63)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=14)</th>
<th>cBMA (N=49)</th>
<th>P-Value</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with Events (%)</td>
<td>2 (14.29%)</td>
<td>12 (24.49%)</td>
<td>.478</td>
<td>1.72 (0.38 - 7.69)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Hazard Ratio (CI) = 1.72 (0.38 - 7.69)  
- p-value = .478

Survival

Hazard Ratio (CI) = 1.72 (0.38 - 7.69)  
p-value = .478  
Censored
## Major Amputation: All Subjects Excluding Rutherford 5 Diabetics

(N=124)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=30)</th>
<th>cBMA (N=94)</th>
<th>P-Value</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with Events (%)</td>
<td>8 (26.67%)</td>
<td>9 (9.57%)</td>
<td>.021*</td>
<td>0.33 (0.13 - 0.84)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Survival Curves]

- Control (N=30)
- MarrowStim (N=94)

Hazard Ratio (CI) = 0.33 (0.13 - 0.84)  
*p-value = .021*  
Censored
Conclusions:

• Excellent safety profile compared to placebo; no statistical difference in total SAEs/AEs between study groups.

• Autologous cBMA improved Amputation Free Survival compared to placebo but not significantly.
  • Statistical power limited by small control population in Rutherford 5 diabetics
  • Actual event rate in control group was 30% vs. predicted 40%

• Post-hoc analyses demonstrate:
  • Significant reduction in major amputation rates in study population when Rutherford 5 diabetics are excluded.