Important RCTs for Venous Wound Healing

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Disclosures

- Veniti Inc.
- Tactile Medical
- Cardinal Healthcare
- Smith and Nephew, Inc

Selected Studies

- RCTs enrolling CEAP class 6 patients in last 2 years
- Outcome measures documenting comparative ulcer healing rates

HP802-247

Allogeneric Living Cell Suspension

- Component 1: Active keratinocytes & fibroblasts in thrombin solution
- Component 2: Fibrinogen solution
- Components sprayed sequentially onto ulcer
- Fibrinogen and thrombin form human fibrin matrix

HP-802 phase IIb Trial Design

- RCT, double blind, N=228
  - vehicle control + 4 dose groups
  - 4 layer compression bandaging for all
- Primary outcome measure
  - Percent healed at 12 weeks

HP802-247 Phase 2(b) Trial Results

Complete Wound Closure at 12 Weeks

% of Patients With Complete Wound Closure
At 12 Weeks, By Dose Group

![Graph showing trial results](image-url)
HP-802 Phase 3

- 440 patient randomized clinical trial
- 80 centers
- Venous ulcers with delayed response to compression
- Randomization
  - Compression and weekly placebo spray
  - Compression plus weekly application of HP-802

HP-802 Phase 3 results

- Failed to achieve primary endpoint
  - Wound closure at 12 weeks
- Living cell therapy did not significantly improve healing compared to standard care alone

Combined Wound Size and Duration

<table>
<thead>
<tr>
<th>Ulcer Score</th>
<th>Ulcer Size and Duration</th>
<th>% Healed, Control</th>
<th>% Healed, Cell therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt; 5 cm^2 And &lt; 6 mos</td>
<td>63%</td>
<td>95%</td>
</tr>
<tr>
<td>1</td>
<td>&gt;5 cm^2 Or &gt; 6 mos</td>
<td>38%</td>
<td>64%</td>
</tr>
<tr>
<td>2</td>
<td>&gt;5 cm^2 And &gt; 6 mos</td>
<td>23%</td>
<td>33%</td>
</tr>
</tbody>
</table>

The Effect of a Connexin43-Based Peptide on the Healing of Chronic Venous Leg Ulcers: A Multicenter, Randomized Trial

- Connexin 43—gap junction protein
  - Key role in control of small molecule signaling to and between cells
  - Regulator of inflammatory cytokine release
  - Mediates fibrosis pathway
  - Controls growth factor response at cellular level
- Concentrations upregulated at wound edge in chronic non-healing wounds

ACT1 peptide - competitive inhibition of Connexin 43

- ACT1 accelerated wound healing in multiple animal model studies
- Phase 2 study initiated Oct 2011
- 92 patients with VLU randomized to:
  - ACT1(topical) in addition to standard of care
  - SOC alone
- SOC included compression bandages, debridement, exudate control

ACT1 for VLU: Results

<table>
<thead>
<tr>
<th>Value</th>
<th>ACT1 + SOC (n=46)</th>
<th>SOC alone (n=46)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% closure at week 12</td>
<td>57%</td>
<td>28%</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean % area reduction at week 12</td>
<td>79%</td>
<td>36%</td>
<td>0.02</td>
</tr>
</tbody>
</table>
**ACT1 VLU results**

- ITT population (n=80)

**Future for Connexin-43 inhibitors**

- Phase 3 studies underway with 2 separate competitive inhibitors studying benefit in accelerating venous leg ulcers
- Successful completion should support FDA approval and additional therapeutic option

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**Simvastatin as a novel therapeutic agent for venous ulcers: a randomized, double-blind, placebo-controlled trial**

M.P. Evangelista, M.F.A. Cancioyan and L.L. Villafuerte

Department of Dermatology, St. Luke’s Medical Center, Baguio Avenue Bo. Cina, Mandaluyong, Philippines

- Potentially beneficial effects of statins in wound healing
  - Reduction of peri-ulcer hypoxia
  - Immunomodulatory effect reducing inflammation
  - May increase epithelial growth by inhibiting glucocorticoid receptors

*Br J Dermatol 2014;170:1151-7*

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**Simvastatin VLU study design**

- Double blind placebo control
- 66 patients randomized to 40 mg QD of simvastatin or placebo
- All patients treated with SOC
  - High strength compression therapy
  - Twice daily saline dressings
- Primary outcome was percent healed at 10 weeks

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**Simvastatin for VLU: results**

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin (n=32)</th>
<th>Placebo (n=34)</th>
<th>P val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound area</td>
<td>37.2 cm²</td>
<td>35.2 cm²</td>
<td>NS</td>
</tr>
<tr>
<td>Wound duration</td>
<td>3.9 years</td>
<td>3.8 years</td>
<td>NS</td>
</tr>
<tr>
<td>% healed at 10 weeks</td>
<td>26 (90%)</td>
<td>11 (34%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Simvastatin VLU: conclusions**

- Improved rate of healing with SOC compared to placebo
- Patient reported QOL significantly better in simvastatin group
- Additional plans for study?
Epifix:

- Human amniotic membrane allograft
- Dehydrated non-viable cellular matrix
  - Comprised of amnion and chorion
  - Contains ECM, growth factors, cytokines
- Shelf life at room temp up to 5 years
- Approved as human cell/tissue based product for use on acute or chronic wounds

Epifix VLU results

- 84 patients with VLUs randomized
  - 53 to compression plus Epifix
  - 31 to compression plus standard dressing
- Primary outcome measure
  - Percent wound closure at 4 weeks
- Percent healed at 4 weeks
  - Epifix grp 48.1%
  - Compression alone 19.0%
- Longer term studies examining ulcer closure rates underway