A Phase 2 Open-Label Single-Arm Study to Assess the Effect of SNF472 on Wound Healing in Calciphylaxis (Calcific Uremic Arteriolopathy) Patients

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Introduction

- **Calcific uremic arteriolopathy (CUA), also called calciphylaxis**
  - Rare, severe form of vascular calcification in patients with ESRD
  - Progressive, painful necrotic skin ulcers resulting from calcification of small vessels
  - 1-year mortality rate of 55% and overall mortality of approximately 80%
  - No approved therapies exist

- **SNF472 is being developed to treat CUA in patients with ESRD on hemodialysis**
  - SNF472 is an intravenous formulation of myo-inositol hexaphosphate (IP6)
  - Selectively inhibits the formation and growth of hydroxyapatite (HAP) crystals, the final common pathway in the pathophysiology of vascular calcification

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Simple and Elegant Physiochemical Mechanism of Action

- SNF472 blocks new Ca-crystal formation and ongoing crystal growth
- Does not interfere directly with calcium and phosphate blood levels
Study Design

Single-arm, Open-label study
• 12-week treatment period and a follow-up visit at Week 13
• SNF472 administered via the dialysis circuit during each dialysis session (3x per week)
  • 400-900 mg based on body weight category
• “Standard of care” CUA treatment per each site’s customary procedures

Key Entry Criteria
• On hemodialysis with newly diagnosed or newly recurrent CUA within 5 weeks of study start
• Diagnosis based on either clinical symptoms or a combination of symptoms and a tissue biopsy

Efficacy Measures
• Would Healing:
  • Bates-Jensen Wound Assessment Tool (BWAT)\(^1\), a validated wound healing assessment tool
  • Qualitative wound image assessments
• Pain: Visual Analog Scale
• Quality of Life: Wound QoL

Study Endpoints

Primary Endpoint – Wound Healing
• Change from Baseline to Week 12 in the total BWAT score

Secondary Endpoints
• Wound Healing:
  • Change from Baseline by visit in the total BWAT score
• Pain:
  • Change from Baseline to Week 12 in the Pain Visual Analog Scale (VAS)
• Quality of Life:
  • Change from Baseline to Week 12 in the Wound Quality of Life (QoL) total score and in the subscales (body, everyday life, psyche)
Wound Healing as Measured with the Bates-Jensen Wound Assessment Tool (BWAT)

- A validated, objective, quantitative tool that can be applied systematically across sites
- Evaluates 13 characteristics of wounds:
  - Size
  - Depth
  - Edges
  - Undermining
  - Necrotic tissue type
  - Necrotic tissue amount
  - Surrounding skin color
  - Exudate type
  - Exudate amount
  - Peripheral tissue edema
  - Peripheral tissue induration
  - Granulation tissue
  - Epithelialization

- Each characteristic is rated on a scale of 1 to 5
- Possible range of total BWAT score is 13 – 65
- BWAT was selected based on regulatory guidance to use a quantitative method to measure wound healing

**Subject Disposition**

<table>
<thead>
<tr>
<th>Population / Disposition</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>Completed study/ Per Protocol</td>
<td>11 (79%)</td>
</tr>
<tr>
<td>Early discontinuation</td>
<td>3 (21%)</td>
</tr>
</tbody>
</table>

**Reasons for discontinuation:**

<table>
<thead>
<tr>
<th>Reason</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject withdrew consent</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Withdrew from dialysis (led to death)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0</td>
</tr>
</tbody>
</table>

ITT, Intent-to-treat population
### Demographics and Baseline Characteristics (ITT Population, N=14)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SE)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 (3.8)</td>
<td>34 - 90</td>
</tr>
<tr>
<td>Years on Hemodialysis</td>
<td>3.8 (1.2)</td>
<td>0.03 - 15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (79)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10 (71)</td>
</tr>
<tr>
<td>American Indian / Alaska Native</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Black / African American</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Baseline Conmeds</td>
<td></td>
</tr>
<tr>
<td>Warfarin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 (14)</td>
</tr>
<tr>
<td>STS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11 (79)</td>
</tr>
</tbody>
</table>

<sup>a</sup>One of the 2 subjects receiving warfarin at baseline stopped warfarin at Week 3.

<sup>b</sup>STS, sodium thiosulfate. 1 additional subject initiated STS at Week 7, 1 subject stopped STS at Week 2, others continued on STS along with SNF472.
Primary Endpoint: Wound Healing Measured by Total BWAT
Statistically Significant Improvement from Baseline to Week 12

ITT (MI), Intent-to-treat population with multiple imputation
Secondary Endpoint: BWAT Over Time
Consistent Reduction in BWAT Score Over Time

Change from Baseline in Total BWAT Score by Week for the Primary Lesion – ITT Observed

Mean (SE) Total BWAT Score

<table>
<thead>
<tr>
<th>Week</th>
<th>No. of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>12</td>
</tr>
<tr>
<td>Week 2</td>
<td>10</td>
</tr>
<tr>
<td>Week 4</td>
<td>10</td>
</tr>
<tr>
<td>Week 6</td>
<td>9</td>
</tr>
<tr>
<td>Week 8</td>
<td>8</td>
</tr>
<tr>
<td>Week 10</td>
<td>8</td>
</tr>
<tr>
<td>Week 12</td>
<td>8</td>
</tr>
<tr>
<td>Follow-up</td>
<td>9 (Week 13)</td>
</tr>
</tbody>
</table>

SNF472

*p<0.05 change from baseline
Secondary Endpoint – Qualitative Wound Image Assessment
Examples of How Experts Evaluated Wound Development

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Baseline</th>
<th>Week 12</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject 1</td>
<td><img src="image1.png" alt="Baseline Image" /> <img src="image2.png" alt="Week 12 Image" /></td>
<td><img src="image2.png" alt="Week 12 Image" /></td>
<td>Improved</td>
</tr>
<tr>
<td>Subject 8</td>
<td><img src="image3.png" alt="Baseline Image" /> <img src="image4.png" alt="Week 12 Image" /></td>
<td><img src="image4.png" alt="Week 12 Image" /></td>
<td>Improved</td>
</tr>
<tr>
<td>Subject 6*</td>
<td><img src="image5.png" alt="Baseline Image" /> <img src="image6.png" alt="Week 12 Image" /></td>
<td><img src="image6.png" alt="Week 12 Image" /></td>
<td>Worsened</td>
</tr>
</tbody>
</table>

*SNF472 plasma concentration was below the limit of quantification in Subject 6 who had significant lesion worsening. Plasma SNF472 was in the expected range in all other subjects.
Secondary Endpoint: Statistically Significant Reduction in Pain from Baseline to Week 12 Using VAS

-23.6 (p=0.015)

ITT (MI) N=14

Mean (SE) VAS Pain

Baseline

Week 12

ITT (MI), Intent-to-treat population with multiple imputation
Secondary Endpoint: Pain VAS Over Time
Consistent Reduction Was Observed from Week 6

Change from Baseline in Pain VAS By Week - ITT (observed)

Mean (SE) VAS Pain

Week 6 20% reduction from baseline
Week 12 31% reduction from baseline

* p<0.05 change from baseline

SNF472
Safety and Tolerability

Adverse Events

• 14 subjects reported 79 treatment-emergent adverse events

Serious Adverse Events and Deaths

• 13 SAEs were reported for 7 subjects, including 2 deaths:
  • Cellulitis, fluid overload, haematemesis, gangrene (wet), gangrene (dry), pulmonary edema, hypertensive emergency, abdominal wound dehiscence, sepsis, urinary tract infection, pyrexial infection due to leg ulcers
  • One death due to cardiogenic shock, one death after withdrawal from hemodialysis (cardiorespiratory arrest)

Laboratory and ECG Data

• No clinically significant changes in any lab or ECG parameter
Conclusions

- This was the first multicenter, international, prospective, interventional study of CUA
- SNF472-treated subjects showed statistically significant and clinically meaningful improvements in wound healing and pain
- SNF472 was generally well tolerated with adverse events consistent with the study population

Perspectives

- A Phase 3 randomized placebo-controlled trial of SNF472 for CUA is in planning stages
- A Phase 2 study to assess the ability of SNF472 to reduce cardiovascular calcification in ESRD is in progress
Thank you!