**Phase 2 Open Label Single Arm Repeat Dose Study to Assess the Effect of SNF472 on Wound Healing in Uraemic Calciphylaxis Patients**

Vincent Brandenburg,1 Smeeta Sinha1, Jose-Vicente Torregrosa2, Carolina Salcedo1, Preston Klassen3, Rekha Gargt,4 Pieter H. Joubert1,4, Joan Perelló4,6

1University Hospital Aachen, Germany, 2Salford Royal NHS Foundation Trust, Salford, United Kingdom, 3D.Nefrologia, Hospital Clinic de Barcelona Barcelona, Spain, 4Sanfillo, Palma, Spain, 5King's College, London, United Kingdom 6Lab. Investigacion in Litiasis Renal, UIB, Palma, Spain

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**Introduction**

Calcific uremic arteriolopathy (CUA), also called calciphylaxis, is a severe form of vascular calcification in patients with end stage renal disease (ESRD).

- Characterized by painful necrotic ulcers or scars resulting from calcification of small peripheral vessels
- Affects up to 4% of patients with ESRD.
- 1-year mortality rate of 35% and overall mortality of approximately 80%, most common due to wound complications.
- No approved therapeutic candidates

SNF472 is being developed to treat CUA in patients with ESRD on hemodialysis.

SNF472 is an intravenous formulation of monomorphic bisphosphonate.

- Selectively inhibits the formation and growth of hydroxyapatite crystals, the final common pathway in the etiology of vascular calcification.

Here we report preliminary interim data from a Phase 2 study to evaluate the effect of SNF472 on top of standard therapy for CUA, wound healing and other parameters of therapeutic response in hemodialysis patients with CUA.

NCT02790073

**Methods**

**Study design**

- Single arm, open label study with a 12 month treatment period and a follow-up visit at Week 12.
- Subjects received infusions of SNF472 via the dialysis circuit during each dialysis session. Each dose was 450mg, based on body weight categories.
- Subjects also received standard of care CUA treatment per each site’s standard procedures.

- Up to 15 subjects could be enrolled.

**Key entry criteria**

- On hemodialysis with either new or recently diagnosed CUA.
- CUA diagnosis based on either discoloration or a combination of symptoms and a tissue biopsy.
- Male:female ratio included 1:1 with weights or of at least 160 lbs.
- Patients scheduled for surgery or dialysis within 7 days of their planned visit were excluded.
- All patients were on dialysis for at least 6 months.

**Endpoint definition**

- Primary endpoint is the absolute change in the Bates-Jerjen Wound Assessment Tool (8WAT) total score from baseline to 12 weeks for each subject.
- Secondary endpoints include changes in 8WAT total and component scores by site, Pain Visual Analog Score (VAS), and Wound Quality of life (QoL), and some subscales.
- Handling of Missing Data: The interim data is based on the last observed value and using LOCF imputation.

**Analysis Populations and Handling of Missing Data**

The interim data analysis was performed on 11 subjects who completed the study.

- The intent-to-treat (ITT) population was the primary efficacy analysis population.
- The per protocol population (PP) was determined using a list of ITT or LOCF and including patients with missing data.

- Sensitivity analyses were conducted to assess the robustness of the results using observed cases and sensitivity analysis.

**Phase 3 randomized controlled trial of SNF472 for CUA is under development**

- SNF472 was generally well tolerated.
- No standardization and stabilization of wound and pain treatment prior to SNF472 treatment initiation or during the study.
- A Phase 3 randomized-controlled trial of SNF472 for CUA is under development.

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**Table 1. Subject Disposition (All Subjects, N=12)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Disposition</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed study/Per Protocol</td>
<td>11 (92%)</td>
<td></td>
</tr>
<tr>
<td>Early discontinuation</td>
<td>1 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>1 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Total lost to follow-up</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Demographic and Baseline Characteristics (ITT, N=12)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>mean (SD)</td>
<td>64.9 (11.7)</td>
</tr>
<tr>
<td>Male</td>
<td>n</td>
<td>10 (83.3)</td>
</tr>
<tr>
<td>Female</td>
<td>n</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>American Indian / Alaska native</td>
<td>n</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>n</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Black</td>
<td>n</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>White</td>
<td>n</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Other</td>
<td>n</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>mean (SD)</td>
<td>81.4 (25.9)</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>mean (SD)</td>
<td>25.9 (4.7)</td>
</tr>
</tbody>
</table>

**Table 3. Improvement in Wound Healing Based on Blinded and Unblinded Qualitative Review of Wound Images**

**Table 4. Serious Adverse Events**

**Figure 1. Wound Healing: Primary Endpoint Met**

**Figure 2. Representative Images of Primary Lesions**

**Figure 3. Statistically Significant Reduction in Pain from Baseline to Week 12 Using VAS**

**Figure 4. Statistically Significant Improvement in Wound QoL, Total and Subscale Scores**

**Results**

- **ITT data**
- **ITT observed data**
- **Independent adjudication**

**Conclusions**

- **SNF472-treated subjects showed:**
  - Statistically significant and clinically meaningful improvements in wound healing and pain
  - Statistically significant reduction in the Wound QoL scale and pain scores
  - Background standard of care for CUA (diabetes duration, diacyl calcium concentration, overall STS use) and for pain were not significantly changed during the study.
  - Treatment-emergent adverse events involving SAEs were consistent with the placebo population overall.

- **SNF472 was generally well tolerated**
- **Limitations of this study:**
  - Single arm, open-label design
  - No standardization and stabilization of wound and pain treatment prior to SNF472 treatment initiation or during the study
  - A Phase 3 randomized-controlled trial of SNF472 for CUA is under development.