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

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Introduction

- Calcific uraemic arteriolopathy (CUA), also called calciphylaxis, is a severe form of vascular calcification in patients with end stage renal disease (ESRD)
  - Characterized by painful necrotic skin ulcers resulting from calcification of small peripheral vessels
  - Affects up to 4% of patients with ESRD
  - 1-year mortality rate of 55% and overall mortality of approximately 80%, most commonly due to wound complications
  - No approved therapies are available
- SNF472 is being developed to treat CUA in patients with ESRD on hemodialysis
  - SNF472 is an intravenous formulation of myo-inositol hexaphosphate
  - 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 of care on promoting wound healing and other parameters of therapeutic response in hemodialysis patients with CUA (NCT02790073; EudraCT 2015-004313-25)

Methods

Study design
- Single arm, open label study with a 12-week treatment period and a follow-up visit at Week 13
- Subjects received infusions of SNF472 via the dialysis circuit during each dialysis session. Each dose was 400-900 mg, 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 clinical symptoms or a combination of symptoms and a tissue biopsy
- Main exclusion criteria included BMI >35 kg/m^2 with presence of central or abdominal skin ulcers, bisphosphonate treatment within the past year, and patients scheduled for a parathyroidectomy at any time during their study participation

Endpoints
- Primary endpoint was the absolute change in the Bates-Jensen Wound Assessment Tool (BWAT) total score from baseline to Week 12 for the primary lesion
- Secondary endpoints included changes in BWAT total and component scores by visit, Pain Visual Analog Scale (VAS), and Wound Quality of Life (QoL) total score and subscales
- SNF472 plasma pharmacokinetics at Day 1 and Week 12

Analysis Populations and Handling of Missing Data
- This interim analysis was performed after 12 subjects completed the study
- The Intent-to-Treat (ITT) population was the primary efficacy analysis population
- Multiple imputation (MI) was the primary method of imputing missing data
- Sensitivity analyses were conducted to assess the robustness of the results using observed cases without imputation and Last Observation Carried Forward (LOCF) method for handling missing data
- The primary endpoint was also analyzed in the Per Protocol population, defined as subjects who received at least 75% of SNF472 doses without major protocol violations

Statistical Comparisons
- Baseline and Week 12 values were compared using a paired student's t-test with no adjustments for multiplicity

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

Population / Disposition	n (%)
ITT	12 (100%)
Completed study/ Per Protocol	9 (75%)
Early discontinuation	3 (25%)
Subject withdrew consent	1 (8%)
Death	1 (8%)
Other	1 (8%)
Adverse event	0
Lost to follow-up	0

ITT, Intent-to-treat population

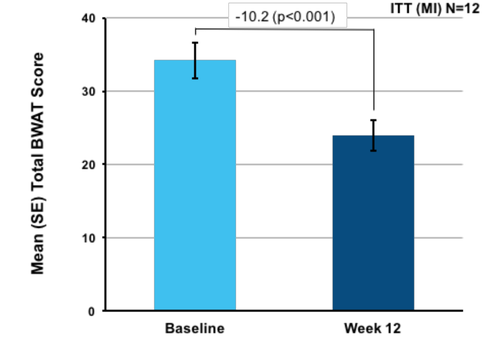
Results

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

Parameter	Statistic	Value
Age (years)	mean (SD)	59.6 (14.9)
	min, max	34, 90
Male / female	n (%)	3 (25%) / 9 (75%)
White	n (%)	8 (66.7%)
American Indian / Alaska Native	n (%)	2 (16.7%)
Black / African American	n (%)	2 (16.7%)
Weight (kg)	mean (SD)	85.79 (25.43)
	min, max	48.6, 136.9
BMI (kg/m^2)	mean (SD)	31.24 (8.89)
category: < 20 / 20-25 / >25	n (%)	1 (8.3%) / 3 (25%) / 8 (66.7%)
Receiving warfarin[a]	n (%)	2 (16.7%)
Receiving STS[b]	n (%)	9 (75.0%)

[a]One of the 2 subjects receiving warfarin at baseline stopped warfarin at Week 3.
[b]STS, sodium thiosulfate. In addition to the 9 subjects receiving STS at baseline, 1 subject initiated STS at Week 7. One subject receiving STS at baseline stopped at Week 2; the others continued STS.

Figure 1. Wound Healing: Primary Endpoint Met Statistically Significant Improvement in Total BWAT Score from Baseline to Week 12



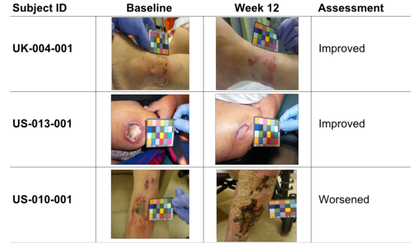
- BWAT, Bates-Jensen Wound Assessment Tool, includes 13 items that assess wound size, depth, edges, undermining or pockets, necrotic tissue type, necrotic tissue amount, exudate type, exudate amount, surrounding skin colour, peripheral tissue edema, peripheral tissue induration, granulation tissue, epithelialization. Each item is rated on a scale of 1 (best) to 5 (worst) and the total score is a sum of these scores.
- Consistent reductions in BWAT from baseline to Week 12 were also seen with the Per Protocol population (p=0.009), ITT observed (p=0.038), and using LOCF imputation (p=0.05).

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

Primary Lesion Rating, Week 12 vs Baseline (N=9)	Blinded n (%)	Unblinded n (%)
Improved	5 (56%)	6 (67%)
Equal	1 (11%)	1 (11%)
Worsened	3 (33%)	2 (22%)

- Nine subjects had images available from baseline and Week 12.
- Two independent reviewers (a wound specialist and a CUA specialist) evaluated standardized lesion images in a blinded (without knowing the order of the visits) and in an unblinded manner (knowing the order).

Figure 2. Representative Images of Primary Lesions



SNF472 plasma concentration was below the limit of quantification in Subject 010-001 who had significant lesion worsening. Plasma SNF472 was in the expected range in all other subjects.

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

- Pain was scored on a visual analog scale (VAS) of 1 to 100
- Consistent reductions in pain were also seen in sensitivity analyses using ITT observed (p=0.023) or LOCF imputation (p=0.027)

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

- The Wound-QoL questionnaire consists of 17 items and 3 subscales measuring disease-specific, health-related quality of life of patients with chronic wounds. Each item is rated on a scale of 0 (best) to 4 (worst) regarding the preceding 7 days. Total score is an average the 17 items.
- Sensitivity analyses using ITT observed or LOCF imputation showed consistent improvements in total QoL scores with p<0.05.

Safety and Tolerability

Adverse Events
- 12 subjects reported 69 treatment-emergent adverse events
- No clustering of adverse events was observed

Serious Adverse Events and Deaths
- 7 subjects reported 14 SAEs
- 2 deaths (cardiogenic shock and cardiopulmonary arrest due to renal failure)
- Events were consistent with the patient population and none were assessed as related by the investigator

Laboratory and ECG Data
- No clinically significant changes in any lab or ECG parameter
- No reductions in ionized calcium were observed (pre- or post-infusion or at end of study)

Table 4. Serious Adverse Events

Event	N=12 n (%)
Subjects with 1 or more SAE	**7 (58.3)**
Hospitalizations	
Nausea	1 (8.3)
Pain in extremity	1 (8.3)
Cellulitis	1 (8.3)
Fluid overload	1 (8.3)
Haematemesis	1 (8.3)
Gangrene (wet)	1 (8.3)
Gangrene (dry)	1 (8.3)
Pulmonary edema	1 (8.3)
Hypertensive emergency	1 (8.3)
Abdominal wound dehiscence	1 (8.3)
Sepsis	1 (8.3)
Urinary tract infection	1 (8.3)
Deaths	
Cardiogenic shock	1 (8.3)
Cardiopulmonary arrest due to renal failure	1 (8.3)

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 subscales
- Background standard of care for CUA (dialysis duration, dialysate calcium concentration, overall STS use) and for pain were not significantly changed during the study
- Treatment-emergent adverse events including SAEs were consistent with the patient population
- 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