Outcomes Assessment in a Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of SNF472 for Treating Calciphylaxis

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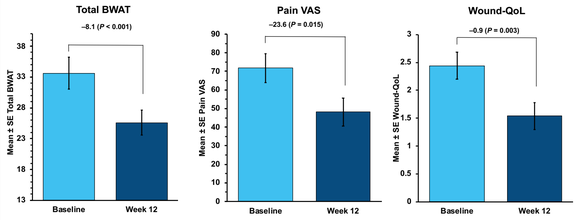
Introduction

- Calcific uremic arteriolopathy (CUA or calciphylaxis) is a severe form of vascular calcification in patients with end-stage renal disease (ESRD)[1]
  - Characterized by painful necrotic skin ulcers resulting from calcification of small peripheral vessels
  - Affects up to 4% of patients with ESRD and has a 1-year mortality rate of 45-55%, most commonly due to wound complications
  - No approved therapies
- The selective calcification inhibitor SNF472, an intravenous formulation of myo-inositol hexaphosphate, inhibits formation and growth of hydroxyapatite crystals to reduce progression of vascular calcification[2,3]
- A recent open-label, single-arm, 12-week, Phase 2 trial of SNF472 in patients with CUA receiving hemodialysis showed improvements in wound healing, pain, and wound-related quality of life (QoL)[4]
- Here we describe the design of CALCIPHYX, a randomized, double-blind, placebo-controlled Phase 3 trial to examine the efficacy and safety of SNF472 for treating CUA

Phase 2 Results

Improvements in Total Bates-Jensen Wound Assessment Tool (BWAT), Pain Visual Analog Scale (VAS), Wound QoL Questionnaire



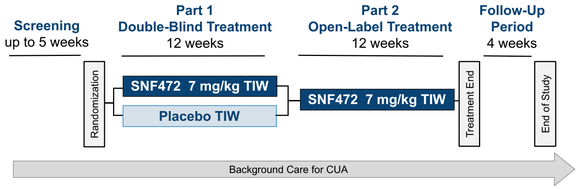
CALCIPHYX Study Objective

To evaluate the efficacy and safety of SNF472 compared with placebo when added to background care for the treatment of CUA

Study Design

Design Overview

- Approximately 66 subjects
- Randomized 1:1 to 7 mg/kg SNF472 or placebo 3x/week during hemodialysis in addition to background care for CUA
  - Randomization stratified by STS use at baseline
- Background care will be in accordance with the clinical practices at each site
  - May include IV sodium thiosulfate (STS)
  - Should be stabilized (including pain medications) during screening
  - No changes should be made after randomization unless medically indicated in the opinion of the site investigator
- SNF472 or matching placebo will be diluted in physiological saline and infused via the dialysis circuit over approximately 2.5 to 3 hours during regularly scheduled dialysis sessions
- 12-week randomized treatment followed by 12-week open-label treatment in which all subjects receive SNF472



Key Inclusion Criteria

- On maintenance hemodialysis for ≥2 weeks prior to screening
- Diagnosis of CUA by the site investigator and ≥1 cutaneous CUA lesion with ulceration of the epithelial surface. A central wound rating group will review wound images to confirm lesion is due to CUA.
- CUA wound-related pain shown by a Pain Visual Analog Scale (VAS) score ≥50 out of 100

Key Exclusion Criteria

- Subjects whose primary (largest) lesion is due to causes other than CUA
- History of treatment with bisphosphonates within 3 months of baseline
- Severely ill subjects without a reasonable expectation of survival for at least 6 months
- Subjects with a scheduled parathyroidectomy
- Participation in an investigational study and receipt of an investigational drug or investigational use of a licensed drug within 30 days prior to screening
  - There is an exception to the 30-day period for IV STS. If participating in an investigational study of IV STS, all visits of that study must be completed prior to screening.

Assessments

Quantitative Wound Evaluation with BWAT and BWAT-CUA

- Bates-Jensen Wound Assessment Tool (BWAT)[5] is a standardized tool for quantitative assessment of wound healing
- The BWAT "total" includes evaluation of 13 items: size, depth, edges, undermining, necrotic tissue type, necrotic tissue amount, exudate type, exudate amount, skin color surrounding wound, peripheral tissue edema, peripheral tissue induration, granulation tissue, and epithelialization
- Each item is rated on a scale of 0 or 1 (best) to 5 (worst)
- Clinicians with combined expertise in CUA and wound healing developed BWAT-CUA[6], a targeted modification of BWAT focusing on prototypical features of CUA:
  - Necrotic tissue type
  - Necrotic tissue amount
  - Exudate type
  - Exudate amount
  - Skin color surrounding wound
  - Peripheral tissue edema
  - Peripheral tissue induration
  - Granulation tissue
- A central wound rating group will determine each BWAT score based on review of standardized wound photos and/or videos, measurements from imaging software, and review of on-site BWAT scores for selected items

Pain VAS

- Electronically administered, requiring the subject to mark a position anywhere on a 100-mm long horizontal line to indicate his/her worst wound-related pain over the last 24 hours

Wound Quality-of-Life Questionnaire

- Measures disease-specific, health-related QoL of patients with chronic wounds
- 17 items on impairments, each rated on a 5-point Likert scale with responses ranging from "not at all" (0) to "very much" (4)

Other Efficacy Assessments

- Qualitative wound image evaluation, wound size, occurrence of new CUA lesions

Safety Assessments

- Adverse events
- Standard safety laboratory measurements
- ECG parameters
- Vital signs

Pharmacokinetics

- Plasma concentration of SNF472 in predose and end-of-infusion (C_{max}) samples

Pharmacodynamics

- Ex vivo method for measuring inhibition of calcification induction in plasma samples

Biomarkers

- Selected biomarkers related to inflammation and calcification

Study Endpoints

Primary Efficacy Endpoints:

- Change from baseline to Week 12 in the BWAT-CUA score for the primary lesion
- Change from baseline to Week 12 in Pain VAS score

Secondary Efficacy Endpoints:

- Change from baseline to Week 12 in the Wound-QoL score
- Change from baseline to Week 12 in the BWAT total score for the primary lesion
- Qualitative wound image evaluation for the primary lesion (worsened, equal to, or improved relative to baseline) at Week 12
- Change from baseline to Week 12 in opioid use as measured in morphine milligram equivalents

Safety Endpoints

- Proportion of subjects with adverse events, serious adverse events, and deaths
- Changes from baseline in laboratory parameters, ECG parameters, and vital signs

Statistical Methods

Planned analyses will use mixed model repeated measures analyses of absolute change from baseline to Week 12 to estimate the difference between randomized treatment groups in efficacy endpoints (eg, BWAT-CUA, BWAT, Pain VAS). The models will include fixed effect terms for randomized treatment group, visit, and visit by randomized treatment group interaction. The models will be stratified for sodium thiosulfate use at baseline and baseline scores (BWAT-CUA, BWAT, Pain VAS) will be included as covariates.

References

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5. Bates-Jensen and Sussman. Tools to measure wound healing. Chapter 5 in Wound Care: A collaborative practice manual for health professionals. Lippincott Williams & Wilkins. Philadelphia, PA. 2012;131-61.
6. Sinha et al. Improvements in calcific uremic arteriolopathy wound healing during SNF472 treatment assessed with the BWAT-CUA. J Am Soc Nephrol. 2018; 29: 914 [abstract].

Trial Information

- This trial is sponsored by Sanifit Therapeutics
- Subject enrollment is expected to begin in Q1 2020
- For more information email: InfoCUAtrial@sanifit.com