Clinical Study Protocol

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of SNF472 When Added to Background Care for the Treatment of Calciphylaxis

SNFCT2017-06

Development Phase	Phase 3
Study Drug	SNF472
Indication	Treatment of calciphylaxis
Sponsor	Sanifit Therapeutics S.A.
EudraCT Number	2018-001301-90
IND Number	116437
Protocol Version and Date	Amendment 3, 9 DEC 2021

Amendment History:

Date	Amendment Number	Region
20 MAY 2019	Original Protocol	Global
17 SEP 2019	01	Global
30 APR 2020	1.1	United Kingdom Specific
10 DEC 2020	1.2	Germany Specific
10 FEB 2021	1.3	Germany Specific
21 MAY 2021	02	Global
9 DEC 2021	03	Global

This study will be conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP), including the archiving of essential documents, and regulatory requirements as applicable.

PROTOCOL AGREEMENT PAGE

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of SNF472 When Added to Background Care for the Treatment of Calciphylaxis

Study SNFCT2017-06 Protocol Amendment 3

Protocol Date: 9 DEC 2021

The undersigned agree that this protocol dated 9 DEC 2021 shall apply to the conduct of the study identified above. By signing below, the Investigator agrees to conduct the study identified above in accordance with the terms set forth herein.

On behalf of Sanifit Therapeutics S.A.:

DocuSigned by:
[redacted]

10-Dec-21 | 05:39:35 PST

Date (DD-MMM-YYYY)

Sanifit Therapeutics S.A.

Site Name or Institution Name (printed)

Investigator Name (printed)

Investigator Signature

Date (DD-MMM-YYYY)

PROTOCOL AMENDMENT 3 - SUMMARY OF CHANGES

1) SYNOPSIS and Section 5.6.1.1: The central wound rating group BWAT Reviewers will not be blinded to the visit order when completing BWAT ratings. BWAT was developed for sequential review of wound images and images can be rated with the greatest accuracy if BWAT reviewers are able to refer to all of a subject's images in chronological sequence.
2) Section 5.6.1.2: Clarification that the qualitative reviewers will not be involved in confirmation of CUA lesions or BWAT rating. These qualitative reviewers are blinded to treatment assignment and visit order in Part 1, and to visit order in Part 2.
3) Section 8.2.2: Clarification that the independent statistical service provider will provide the conditional power and sample size computations to the independent DSMB only. The DSMB will review the results and then provide only the sample size recommendation to the Sponsor.

PROTOCOL SYNOPSIS

Study Title:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of SNF472 When Added to Background Care for the Treatment of Calciphylaxis

Protocol Number: SNFCT2017-06

Indication: Treatment of calciphylaxis (calcific uremic arteriolopathy [CUA])

Sponsor: Sanifit Therapeutics S.A.

Number of Subjects and Study Sites: Planned enrollment is approximately 66 subjects from approximately 60 sites in multiple countries. Number of subjects may be adjusted up to a maximum of 99 based on results of a sample size re-estimation (SSRE).

Study Objectives

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

Study Design and Methodology

This Phase 3, global, multicenter study will examine the efficacy and safety of SNF472 in adult subjects on maintenance hemodialysis (HD) who have at least one ulcerated CUA lesion (wound). The study will include a screening period of up to 5 weeks, a 12-week double-blind, randomized, placebo-controlled treatment period (Part 1) followed by a 12-week open-label treatment period (Part 2), and a 4-week follow-up period.

Screening Period: Informed consent will be obtained prior to performing any study procedures. Subject eligibility will be evaluated during the screening period, which will be conducted as a two-step process. In addition, the subject's pain medications will be stabilized between Screening Visit 1 and Screening Visit 2 to determine the baseline maintenance pain medication dose. Completion of screening within 4 weeks or less is preferred but up to 5 weeks is allowed.

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to receive either 7 mg/kg of SNF472 or matching placebo in a double-blind manner. Randomization will be stratified based on intravenous STS use at the time of randomization (yes/no).

Double-blind, Randomized, Placebo-Controlled Treatment Period (Part 1): Subjects will receive SNF472 or placebo for 12 weeks in addition to background care (in accordance with the clinical practices of each site). No changes to the background care regimen, including pain

medication, should be made after randomization unless medically indicated in the opinion of the Investigator.

The Schedule of Events for the Screening Period and Part 1 is provided in Table 1.

Open-label Treatment Period (Part 2): Subjects who complete Part 1 will be eligible to participate in Part 2, in which all subjects will receive open-label SNF472 for 12 weeks and continue stable background care (in accordance with the clinical practices of each site), including pain medication, with no changes unless medically indicated in the opinion of the Investigator.

The Schedule of Events for Part 2 and the follow-up visit is provided in Table 2.

Follow-Up Period/ Early Termination: Subjects completing the study will return for a follow-up visit 4 weeks after the last dose of study drug. Subjects should continue on stable background care, including pain medication, during the 4-week follow-up period. with no changes unless medically indicated in the opinion of the Investigator. Subjects who discontinue study drug during Part 1 or Part 2 will be asked to complete study assessments throughout the respective part of the study (Part 1 or Part 2) and complete a follow-up visit.

Subjects will record all pain medications used in a pain medication diary throughout Screening, Part 1, Part 2, and the follow-up period. Diaries should be reviewed with the subject at least weekly and pain medications will be recorded in the electronic case report form (eCRF).

The following assessments will be performed during this study: demographic characteristics, medical history, prior/concomitant medications, physical examination, body weight, vital signs, electrocardiograms (ECGs), Holter monitoring, blood samples for central laboratory assessments (hematology, chemistry, ionized calcium, parathyroid hormone [PTH], high-sensitivity C-reactive protein [hs-CRP], and serum pregnancy test [females of childbearing potential only]), dialysis parameters, record CUA wound care, wound imaging (photos and video) and assessment (including Bates-Jensen Wound Assessment Tool [BWAT], qualitative wound evaluation, occurrence of new CUA lesions), Pain Visual Analog Scale (VAS), Wound-Quality of Life [Wound-QoL] questionnaire, review of subject diary of pain medications, adverse events (AEs), HD-related events, and blood samples for pharmacokinetics (PK), pharmacodynamics (PD), and biomarkers. No DNA testing will be performed.

All 13 items comprising the “BWAT total” score will be assessed: 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. Endpoints will include the BWAT total score as well as a targeted modification of BWAT, the “BWAT-CUA”, which focuses on the following 8 prototypical features of CUA lesions: necrotic tissue type, necrotic tissue amount, exudate type, exudate amount, skin color surrounding wound, peripheral tissue edema, peripheral tissue induration, and granulation tissue. Sites will capture photos and videos of the wounds using the provided device and imaging software and will receive training on BWAT and rating of undermining, peripheral tissue edema, and peripheral tissue induration. An expert central wound rating group blinded to treatment will perform a quality review of the site’s ratings and rate the remaining BWAT items based on review of the wound photos and videos, aided by automated

measurements from imaging software for the wound size assessment. If a subject has more than one CUA lesion, the course of up to 3 of these (primary, secondary, tertiary) will be assessed with BWAT. Designation of lesions as primary, secondary, and tertiary will be defined based on the total area measured by the wound imaging software at screening. The progress of the primary lesion will also be evaluated with a qualitative review by the central wound rating group.

Pain VAS will be electronically administered, requiring the subject to mark a position on a 10-cm long horizontal line to indicate the worst wound-related pain experienced during the previous 24 hours.

The Wound-QoL questionnaire will also be electronically administered and consists of 17 questions on impairments that are assessed in reference to the preceding 7 days.

Safety information from this study will be reviewed by an external independent Data and Safety Monitoring Board (DSMB).

Study Duration

The planned length of participation in the study for each subject is up to approximately 33 weeks (from screening through completion of the follow-up visit). This includes:

- Screening period of up to 5 weeks
- Part 1 treatment period of 12 weeks
- Part 2 treatment period of 12 weeks
- Follow-up period of 4 weeks

Test Product and Reference Therapy, Dose and Mode of Administration

The test product, SNF472, will be supplied as a 30mL sterile vial containing 30 mg/mL solution (900 mg) in a blinded manner for Part 1 and in an unblinded manner for Part 2. Subjects randomized to active treatment for Part 1 will receive 7 mg/kg of SNF472 three times weekly (TIW) during dialysis sessions. All subjects will receive 7 mg/kg of SNF472 TIW during dialysis sessions for Part 2.

Placebo will be supplied in a blinded fashion as a physiological saline solution in a 30 mL sterile vial that is identical in appearance to the SNF472 test product. Subjects randomized to placebo for Part 1 will receive placebo TIW during dialysis sessions.

In Part 1, weight for dosing calculation will be the subject's body weight recorded after hemodialysis during screening. In Part 2, weight for dosing calculation will be the subject's body weight recorded after hemodialysis at Week 12 Day 5.

SNF472 solution and placebo will be diluted in physiological saline and infused via the dialysis circuit over a period of approximately 2.5 – 3 hours.

Summary of Eligibility Requirements

Inclusion Criteria

1. ≥18 years of age
2. Receiving maintenance HD in a clinical setting for at least 2 weeks prior to screening
3. Clinical diagnosis of CUA by the Investigator including ≥1 CUA lesion with ulceration of the epithelial surface. A central wound rating group will review wound images to confirm the primary lesion is due to CUA.
4. CUA wound-related pain shown by a Pain VAS score ≥50 out of 100
5. Primary lesion that can be clearly photographed for the purpose of protocol-specified wound healing assessments
6. Willing and able to understand and sign the informed consent form and willing to comply with all aspects of the protocol

Exclusion Criteria

1. Subjects whose primary lesion is due to causes other than CUA
2. History of treatment with bisphosphonates within 3 months of baseline (Week 1 Day 1)
3. Severely ill subjects without a reasonable expectation of survival for at least 6 months based on the assessment of the Investigator
4. Subjects with a scheduled parathyroidectomy during the study period
5. Expectation for kidney transplant within the next 6 months based on Investigator assessment or identification of a known living donor
6. Pregnant or trying to become pregnant, currently breastfeeding, or of childbearing potential (including perimenopausal women who have had a menstrual period within one year) and not willing to either completely avoid sexual intercourse with a person of the opposite sex or use a highly effective method of birth control (specified in Section 4.7.4.2) from screening through at least 30 days after last dose of study drug
7. Significant noncompliance with dialysis treatment evidenced by repeated missed dialysis sessions (including if due to hospitalizations where dialysis treatment is unavailable) or significant noncompliance with medication regimen, in the judgment of the Investigator
8. Any history of active malignancy within the last year (history of localized basal cell or squamous cell carcinoma that has been excised/appropriately treated or a fully excised malignant lesion with a low probability of recurrence will not be considered exclusionary)
9. Clinically significant illness other than CUA within 30 days prior to screening that, in the judgment of the Investigator, could interfere with interpretation of study results, impair compliance with study procedures, or impact the safety of the subject (e.g., unstable angina, unstable heart failure, stroke, uncontrolled hypertension, or other illness requiring hospitalization)
10. Participation in an investigational study and receipt of an investigational drug or investigational use of a licensed drug (with the exception of intravenous STS) within 30 days prior to screening. If participating in an investigational study of intravenous STS,

all visits of that study must be completed prior to screening for this study. *Note: Off-label use of intravenous STS outside of an investigational study is not restricted.*

11. Past or current participation in another clinical study with SNF472
12. History or presence of active alcoholism or drug abuse as determined by the Investigator within 6 months before screening or concurrent social conditions that, in the opinion of the Investigator, would potentially interfere with the subject's study compliance
13. Mental impairment or history of or current significant psychiatric disease that, in the opinion of the Investigator, may impair ability to provide informed consent or impact compliance with study procedures
14. Any other condition or circumstance that, in the opinion of the Investigator, may make the subject unlikely to complete the study or comply with study procedures and requirements, or may pose a risk to the subject's safety and well-being
15. Subjects whose CUA lesions exhibit significant improvement, in the opinion of the Investigator, between the first and second screening visit

Study Endpoints

Efficacy Endpoints:
In Part 1, the primary, secondary, and exploratory efficacy endpoints will compare the placebo and SNF472 groups as follows.

Alternate Primary Efficacy Endpoints:

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

Secondary Efficacy Endpoints (assessed hierarchically):

- Absolute change from baseline to Week 12 in the Wound-QoL score
- Absolute 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
- Rate of change in opioid use as measured in morphine milligram equivalents (MME) from baseline to Week 12

Exploratory Efficacy Endpoints:

- Absolute change from baseline to Week 12 in wound size for the primary lesion
- Absolute change from baseline to Week 12 in each BWAT item for the primary lesion
- Absolute change in BWAT-CUA, BWAT total, Pain VAS, and Wound-QoL score by visit
- Proportion of subjects with new CUA lesions between baseline and Week 12
- Absolute change from baseline to Week 12 in the Wound-QoL scores for the body, everyday life, and psyche subscales

- Absolute change from baseline to Week 12 in the BWAT-CUA score for the secondary and tertiary lesions
- Proportion of subjects requiring an increase in pain medication related to their CUA lesion(s) between baseline and Week 12
- Proportion of subjects with a decrease in pain medication related to their CUA lesion(s) between baseline and Week 12
- Absolute change from baseline to Week 12 in opioid use as measured in MME

Additional exploratory endpoints for Part 2 are described in Section 8.1.1.

Safety Endpoints:

- Proportion of subjects with AEs, SAEs, and deaths
- Changes from baseline in the following:
  - Laboratory parameters
  - Holter monitoring results
  - QTc interval and other ECG parameters
  - Vital signs
- Proportion of subjects with a CUA wound-related infection, sepsis, hospitalization, or any CUA wound-related complication

Statistical Methods

Alternate Primary Endpoints

The comparison of absolute change from baseline to Week 12 in BWAT-CUA score between treatment groups will be achieved using a mixed model repeated measures (MMRM) analysis to estimate the difference between randomized treatment group least squares means (LS means) at 12 weeks. The model will include fixed effect terms for randomized treatment group, visit, and visit by randomized treatment group interaction. The model will be stratified for STS use at randomization and baseline BWAT-CUA score use will be included as a covariate. Subject will be fitted as a random effect and an unstructured variance-covariance matrix will be used.

The comparison of absolute change from baseline to Week 12 in Pain VAS will be analyzed using an MMRM analysis similar to that for the change in BWAT-CUA score with covariates of baseline Pain VAS and stratified for STS use at randomization.

Secondary Efficacy Endpoints

The secondary endpoints will be evaluated hierarchically. The first secondary efficacy endpoint of the absolute change from baseline to Week 12 in Wound-QoL score will be analyzed using an MMRM analysis similar to that for the alternate primary efficacy endpoints with baseline Wound-QoL score as a covariate and stratified for STS use at randomization. The second secondary efficacy endpoint of the absolute change from baseline to Week 12 in the BWAT total score will be analyzed using an MMRM analysis with baseline BWAT total score as a covariate and stratified by STS use at randomization. The third secondary endpoint of qualitative wound image evaluation for the primary lesion at Week 12 will be analyzed using generalized estimating equations. Results will be displayed in terms of the odds ratio of SNF472 vs placebo along with the associated 95% CI and 2-sided p-value. The fourth secondary endpoint of rate of change in opioid use from baseline to Week 12 will be analyzed via a mixed model random coefficients analysis.

Overall Type I Error Control

To prevent any overall Type I error inflation, the alternate primary endpoints will be assessed using a Hochberg procedure with a 2-sided alpha level of 4%. If both alternate primary endpoints are met, the alpha apportioned will be recycled so that the secondary endpoints will be assessed hierarchically at the 5% alpha level, 2-sided. If only one alternate primary endpoint is met, the secondary endpoints will be assessed hierarchically at the 1% alpha level, 2-sided.

Sample Size Re-estimation

A SSRE procedure is planned when primary endpoint data is available from approximately 33 of the planned total of 66 subjects randomized and treated for 12 weeks. This procedure will be conducted blind to the sponsor by an external independent statistical service provider. Any increase in sample size with be capped at 50% of the planned sample size (i.e., the maximum total sample size will be capped at 66 + 1/2 x 66 = 99 subjects). Details are provided in Section 8.2.2.

Safety Data

Safety data will be analyzed descriptively and will include frequencies of AEs, serious AEs (SAEs), deaths, and wound-related complications. Summaries of changes from baseline in laboratory parameters, Holter monitoring, QTc interval and other ECG parameters, and vital signs will be provided.

SCHEDULE OF ASSESSMENTS

Table 1. Schedule of Events for Part 1

	SCREENING PERIOD up to 5 weeks		PART 1																																
Week			**1**			**2**			**3**			**4**			**5**			**6**			**7**			**8**			**9**			**10**			**11**			**12**		
Day[1]	**SV1**	**SV2**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**
Informed consent[2]	X																																				
Inclusion/exclusion[3]	X																																				
Review CUA wounds for significant improvement		X																																			
Demographics, medical history	X																																				
Randomization[4]		X																																			
Prior/concomitant medications[5]	X	X	X				X			X			X			X			X			X			X			X			X			X			X		(X)
Pain medication diary[6]	X	X	X				X			X			X			X			X			X			X			X			X			X			X		(X)

[1] Complete procedures scheduled for Week 1 on Day 1. A ± 2-day visit window is allowed for Weeks 2 through 11, with assessments on Day 3 preferred. For Week 12, assessments on Day 5 are preferred, however, a window of -2 days to +3 days is allowed.
[2] Informed consent will be obtained prior to performing any study procedures.
[3] The inclusion/exclusion criteria will be assessed for each subject at screening. A central wound rating group will review wound images to confirm the primary lesion is due to CUA.
[4] Randomization will occur at SV2 which may be up to one week prior to Week 1 Day 1.
[5] At screening, medications taken during the past 30 days will be recorded as prior medications. New medications and/or changes in ongoing prior medications relative to screening will be documented before the first dose of study drug on Week 1 Day 1. After the first dose of study drug, new medications and/or changes to ongoing medications will be recorded as concomitant medications.
[6] Subjects should be instructed to enter pain medications taken into the diary on a daily basis and bring their diary with them to the site at each visit. Site should check at each visit that the diary is being completed. At least weekly, the site should review the diary with the subject and record the pain medications used in the eCRF.

	SCREENING PERIOD up to 5 weeks		PART 1																																		
Week			**1**			**2**			**3**			**4**			**5**			**6**			**7**			**8**			**9**			**10**			**11**			**12**		
Day[1]	**SV1**	**SV2**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**
Record CUA wound care			X				X			X			X			X			X			X			X			X			X			X					(X)
Physical exam[7]	X																																						(X)
Vital signs[8]	X		X																X																				(X)
Holter[9]		X	X																X																				(X)
ECG[10]		X X	X X																																				(X) (X)
Ionized calcium[11] (pre-dose & EOI)			X X																X X																				(X) (X)
Hematology, and chemistry[12]	X		X																X																				(X)
PTH[13]			X																																				(X)
Serum pregnancy[14]		X																																					(X)

[7] Physical exam including weight recorded after hemodialysis without shoes. If body weight cannot be assessed without shoes, it should be assessed under the same conditions throughout the study. Physical exam at SV1 also includes measurement of height.

[8] Vital signs (heart rate, systolic and diastolic blood pressures, respiratory rate, and body temperature) will be assessed post-dialysis after the subject has been sitting for 5 minutes. The results of these protocol-specified assessments will be recorded in the eCRF; however, additional vital sign assessments taken as part of standard care do not need to be recorded.

[9] The Holter monitor will be placed on the subject at least 30 min prior to the beginning of dialysis. The SV2 Holter may be conducted at any dialysis session during the last week of screening prior to Week 1 Day 1 The recording window will be from 30 min prior to the beginning of dialysis until the end of dialysis.

[10] Local ECGs will be assessed for abnormalities by the Investigator. SV2 ECGs should be recorded at the start of dialysis and 2.5 hours after the start of dialysis and may be conducted at any dialysis session during the last week of screening prior to Week 1 Day 1. ECGs at Weeks 1 and 12 should be recorded pre-dose and EOI (within 20 minutes prior to the end of the study drug infusion).

[11] Blood samples will be collected via the dialysis port pre-dose and EOI (within 20 minutes prior to the end of the study drug infusion). Ionized calcium samples must be shipped on day of collection under ambient conditions to the central laboratory.

[12] Blood samples will be collected via the dialysis port. At SV1, collect hematology and chemistry samples at the start of dialysis after notification through the IRT that the subject's lesion(s) and Pain VAS score have met eligibility requirements. Collect samples pre-dose at Weeks 1, 6, and 12.

[13] Blood samples will be collected pre-dose via the dialysis port.

[14] Females of childbearing potential only. Blood sample for pregnancy testing must be collected within 7 days prior to the first dose of study drug.

	SCREENING PERIOD up to 5 weeks		PART 1																																				
Week			**1**			**2**			**3**			**4**			**5**			**6**			**7**			**8**			**9**			**10**			**11**			**12**		
Day[1]	**SV1**	**SV2**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**
Study drug administration[15]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Dialysis parameters[16]	X		X																X																					(X)
Photo/video collection & BWAT[17]	X		X				X						X						X						X					X									(X)
New CUA lesions[18]																			X																					(X)
Pain VAS	X		X				X						X						X						X					X									(X)
Wound-QoL	X		X				X						X						X						X					X									(X)
Biomarkers[19] (pre-dose & EOI)			X X																																					(X) (X)
PK and PD[19] (pre-dose & EOI)			X X																																					(X) (X)
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
HD-related events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)

BWAT=Bates Jensen Wound Assessment Tool; ECG=electrocardiogram; EOI=end of infusion; HD=hemodialysis; IRT=Interactive Response Technology; Kt/V=urea clearance x time / total body water volume; MME=morphine milligram equivalents; PD=pharmacodynamic; PK=pharmacokinetic; PTH=parathyroid hormone; QoL=quality of life; SV=screening visit; URR=urea reduction ratio; VAS=Visual Analog Scale.

[15] Study drug will be administered 3 times weekly (TIW) during dialysis sessions.
[16] Record calcium concentration in the dialysate, dialysis frequency and duration, and Kt/V or URR. Estimated Kt/V or URR from the dialysis machine or calculated values using local lab measurements may be collected. For each subject, the same measure (Kt/V or URR) should be recorded at each visit and it should be based on the same data source (dialysis machine or calculation using local labs) throughout the study.
[17] Rate undermining, peripheral tissue edema, and peripheral tissue induration and collect images (photos and videos) of primary, secondary, and tertiary CUA lesions (as specified in the Site Imaging and BWAT Manual) for evaluations to be performed by the central wound rating group.
[18] Collect images of suspected CUA lesions that were not present at baseline (Week 1 Day 1).
[19] Blood samples will be collected via the dialysis port at pre-dose and EOI (within 20 minutes prior to the end of the study drug infusion).

Table 2. Schedule of Events for Part 2 and Follow-Up

	PART 2																																	FU/ ET[1]
Week	13			14			15			16			17			18			19			20			21			22			23			24			
Day[2]	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	
Concomitant medications[3]	X				X			X			X			X			X			X			X			X			X			X			(X)	X
Pain medication diary[4]	X				X			X			X			X			X			X			X			X			X			X			(X)	X
Record CUA wound care	X				X			X			X			X			X			X			X			X			X			X			(X)	X
Physical exam[5]																																					(X)	X
Vital signs[6]																	X																				(X)	X
Holter[7]	X																																				(X)	
ECG[8] (pre-dose & EOI)	X X																																				(X) (X)	

[1] Subjects completing the study should return for a follow-up visit 4 weeks after the last dose of study drug. Subjects who discontinue study drug during Part 1 or Part 2 will be asked to complete study assessments throughout the respective part of the study (Part 1 or Part 2) and complete the follow-up visit. Subjects who discontinue study drug and are unwilling to complete the remaining study assessments will be encouraged to return for an early termination visit 4 weeks after the last dose of study drug.

[2] Week 13 visit should occur on Day 1. A ±2-day visit window is allowed for Weeks 14 through 23. For Week 24, assessments on Day 5 are preferred, however, a window of -2 days to +3 days is allowed.

[3] Record concomitant medications on Week 13, Day 1 and new medications and/or changes in concomitant medications thereafter.

[4] Subjects should be instructed to enter pain medications taken into the diary on a daily basis and bring their diary with them to the site at each visit. Site should check at each visit that the diary is being completed. At least weekly, the site should review the diary with the subject and record the pain medications used in the eCRF.

[5] Physical exam including weight recorded after hemodialysis without shoes. If body weight cannot be assessed without shoes, then it should be assessed under the same conditions throughout the study.

[6] Vital signs (heart rate, systolic and diastolic blood pressures, respiratory rate, and body temperature) will be assessed post-dialysis after the subject has been sitting for 5 minutes. The results of these protocol-specified assessments will be recorded in the eCRF; however, additional vital sign assessments taken as part of standard care do not need to be recorded.

[7] The Holter monitor will be placed on the subject and the recording started at least 30 min prior to the beginning of dialysis. The recording window will be from 30 min prior to the beginning of dialysis until the end of dialysis.

[8] Local ECGs will be assessed for abnormalities by the Investigators and should be recorded pre-dose and EOI (within 20 min prior to the end of the study drug infusion).

	PART 2																																				FU/ ET[1]
Week	13			14			15			16			17			18			19			20			21			22			23			24			
Day[2]	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	
Ionized calcium[9] (pre-dose & EOI)	X X																X X																				(X) (X)	
Hematology, chemistry[10]																	X																				(X)	X
PTH[11]																																					(X)	X
Serum pregnancy[12]																																					(X)	X
Study drug administration[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	
Dialysis parameters[14]																	X																				(X)	X
Image/video collection & BWAT[15]					X						X						X						X						X								(X)	X
New CUA lesions[16]																	X																				(X)	X
Pain VAS					X						X						X						X						X								(X)	X

[9] Blood samples will be collected at pre-dose and EOI (within 20 minutes prior to the end of the study drug infusion) via the dialysis port. Ionized calcium samples must be shipped on day of collection under ambient conditions to the central laboratory.
[10] Blood samples will be collected via the dialysis port. Collect samples pre-dose at Week 18 and Week 24. For the FU/ET visit, collect sample at the start of dialysis.
[11] Blood samples will be collected via the dialysis port. Collect sample pre-dose at Week 24. For the FU/ET visit, collect sample at the start of dialysis.
[12] Females of childbearing potential only.
[13] Study drug will be administered 3 times weekly (TIW) during dialysis sessions.
[14] Record calcium concentration in the dialysate, dialysis frequency and duration, and Kt/V or URR. Estimated Kt/V or URR from the dialysis machine or calculated values using local lab measurements may be collected. For each subject, the same measure (Kt/V or URR) should be recorded at each visit and it should be based on the same data source (dialysis machine or calculation using local labs) throughout the study.
[15] Rate undermining, peripheral tissue edema, and peripheral tissue induration and collect photos and videos of primary, secondary, and tertiary CUA lesions (as specified in the Site Imaging and BWAT Manual) for evaluations to be performed by central wound rating group.
[16] Collect images of suspected CUA lesions that were not present at baseline (Week 1 Day 1).

	PART 2																																				FU/ ET[1]
Week	13			14			15			16			17			18			19			20			21			22			23			24			
Day[2]	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	
Wound-QoL					X						X						X						X						X							(X)	X
Biomarkers[17]	X X																																			(X) (X)	X
PK and PD (pre-dose & EOI)[18]	X X																																			(X) (X)	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X
HD-related events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X

BWAT=Bates Jensen Wound Assessment Tool; ECG=electrocardiogram; EOI=end of infusion; ET=early termination; FU=follow up; HD=hemodialysis; Kt/V=urea clearance x time / total body water volume; QoL=quality of life; PD=pharmacodynamic; PK=pharmacokinetic; PTH=parathyroid hormone; URR=urea reduction ratio; VAS=Visual Analog Scale.

[17] For Weeks 13 and 24 biomarker samples will be collected via the dialysis port at pre-dose and EOI (within 20 minutes prior to the end of the study drug infusion). For the FU/ET visit the biomarker sample should be collected at the start of dialysis.

[18] PK and PD samples will be collected via the dialysis port at pre-dose and EOI (within 20 minutes prior to the end of the study drug infusion).

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the time-concentration curve
BLQ	below the limit of quantitation
BWAT	Bates Jensen Wound Assessment Tool
C_{max}	observed maximum concentration
CRO	contract research organization
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CUA	calciphylaxis (calcific uremic arteriolopathy)
CVC	cardiovascular calcification
CYP	cytochrome p450
DMP	data management plan
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOI	end of infusion
ESRD	end-stage renal disease
ET	early termination
FDA	Food and Drug Administration
FGF23	fibroblast growth factor 23
GCP	Good Clinical Practice
GDF15	growth differentiation factor 15
GLP	Good Laboratory Practice
HAP	hydroxyapatite
HD	hemodialysis
IC_{50}, IC_{65}, IC_{80}	50%, 65%, and 80% maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	Independent Ethics Committee
IP6	myo-inositol hexaphosphate (phytate)

IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IV	Intravenous
Kt/V	urea clearance x dialysis time / total body water volume
LS mean	least squares mean
MGP	matrix gla protein
mITT	modified Intent-to-treat
MME	morphine milligram equivalents
MMRM	mixed model repeated measures
N	count
PD	pharmacodynamics
PIL	patient information leaflet
PK	pharmacokinetics
PP	per protocol
PTH	parathyroid hormone
Q1, Q3	first quartile, third quartile
QoL	quality of life
QTc, QTcF	corrected QT interval, QT interval corrected by Fridericia's formula
SAE	serious adverse event
Sanifit	Sanifit Therapeutics S.A. (Sponsor)
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
SSRE	sample size re-estimation
STS	sodium thiosulfate
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TIW	3 times weekly
URR	Urea reduction ratio
US	United States
VAS	Visual Analog Scale
VSMC	vascular smooth muscle cells

1 INTRODUCTION

1.1 INDICATION/BACKGROUND TO THE DISEASE

1.1.1 Calciphylaxis

Calciphylaxis is a rare disease seen predominantly in patients receiving dialysis. As of 31 December 2015, the number of patients on dialysis was approximately 430,519 in Europe and 492,227 in the United States (US) (European Renal Association – European Dialysis and Transplant Association Registry, 2017; United States Renal Data System, 2017). Calciphylaxis in the end-stage renal disease (ESRD) population is also known as calcific uremic arteriolopathy [CUA]. The estimated prevalence of CUA is between 1% and 4% of the ESRD population (Goel et al, 2011; Nunley, 2017; Schlieper et al, 2009), suggesting a prevalence of 4,305 to 17,221 in Europe and 4,923 to 19,691 in the US. In addition, recent estimates of incidence of CUA have been reported as <1500 patients on dialysis in the US based on sodium thiosulfate (STS) use, 0.12% of dialysis patients per year in the United Kingdom (UK Registry, personal communication with Smeeta Sinha), and 0.04% of dialysis patients per year in Germany (Brandenburg et al, 2017).

Calciphylaxis in patients with ESRD is a life-threatening condition with 1-year mortality rates of 45-55% (McCarthy et al, 2016; Nigwekar et al, 2016; Weenig et al, 2007). In addition, a high rate of mortality was observed within the first few months after diagnosis of CUA (Mazhar et al, 2001). Major surgical interventions are common in these patients with one study reporting that 69% of patients required extensive debridement, revascularization, or amputation (Obialo and Quarshi 2017).

The disease is characterized by accelerated soft tissue calcification, including calcification and thrombosis of smaller arteriolar vessels, leading to progressive and painful necrotic skin ulcerations (Nigwekar et al, 2018). The pathophysiology of CUA involves the deposition of calcium in the tunica media of smaller arteriolar vessels. The deposition of calcium is accompanied by local inflammation and arteriolar thrombosis, leading to regional ischemia and subsequent necrosis of subcutaneous fat and the overlying skin. The skin and subcutaneous lesions of CUA are the primary manifestation of the disease. Lesions most commonly appear in the lower extremities and in the trunk, particularly in the abdomen. Less commonly reported locations include the arms, hands and fingers, buttock/hip, chest, and genitals (Chinnadurai et al 2021; Weenig et al, 2007) On palpation, skin and soft tissue surrounding necrotic areas often show a characteristic plaque-like hardening. The progressive, ischemic ulcers are extremely painful, and patients often require opioids for pain control. In addition to the pain, these patients have an increased susceptibility to wound infection, which is ultimately responsible for over 50% of the mortality (Weenig et al, 2007).

In these patients, calcification of arterial walls and heart valves leads to coronary heart disease, heart failure, myocardial infarction and cardiovascular events, which are often fatal. While much remains unclear about the triggers for the pathogenic process of CUA, the vascular deposition of calcium appears to be a necessary, but possibly not a sufficient, factor in development of the full clinical profile. A diagnosis can be made based on clinical characteristics

and can be confirmed by a skin biopsy which shows arterial calcification and occlusion in the absence of vasculitis.

1.1.2 Current CUA Care

There are currently no approved medicinal products or devices for the treatment of CUA, and no specific guidelines. Current care relies on 1) reducing clinical factors that may exacerbate the deposition of calcium in vascular tissue, 2) wound care, and 3) control of pain (Goel et al, 2011; Seethapathy et al, 2019). Clinical interventions aimed at reducing the impact of CUA are listed below.

- Topical wound care with measures to prevent infection
- Pain management
- Elimination of potential precipitating factors such as Vitamin K antagonist-based anticoagulation (e.g., warfarin, as a reduction in vitamin K appears to promote calcium deposition)
- Avoidance of calcium-based phosphate binder therapy
- Reduction in vitamin D administration (as vitamin D appears to promote calcium deposition)
- Use of low calcium concentration in the dialysis bath
- Patients on peritoneal dialysis might benefit from switching to HD (Fine and Fontaine, 2008) with a low calcium dialysate.
- Intensification of dialysis prescription
- Treatment with calcimimetics such as cinacalcet or etelcalcetide (Robinson et al, 2007)
- Parathyroidectomy
- Hyperbaric oxygen might relieve ischemic features (Podymow et al, 2001).
- Bisphosphonates
- Use of STS for pain control and potentially a reduction in calcium deposition

None of the therapeutic interventions listed above have been subjected to adequate evaluation in controlled clinical trials. STS is widely used off-label for treatment of CUA although evidence supporting its efficacy is largely limited to retrospective chart reviews (Nigwekar et al, 2013) and case reports (Peng et al, 2018; Smith et al, 2012). Calcium-chelation, direct vascular calcification inhibitory effects, antioxidant effects, and vasodilatory properties have all been proposed as mechanisms through which STS may improve CUA (as reviewed, O'Neill 2013).

1.2 SNF472

SNF472 is a selective calcification inhibitor that works by binding to the growth sites of the hydroxyapatite (HAP) crystals. Chemically, SNF472 is the hexasodium salt of myo-inositol hexaphosphate (IP6, phytate).

SNF472 is being developed by Sanifit Therapeutics S.A. (Sanifit) for the treatment of CUA and cardiovascular calcification (CVC) in patients with ESRD undergoing HD.

Multiple mechanisms lead to the formation and growth of calcified deposits in arterioles and other small vessels, which appear to be fundamental to the development of CUA. SNF472 is a novel entity with a new mechanism of action selectively directed to inhibit the final and common step in the pathway of vascular calcification by chemically blocking calcium crystal formation and growth. Regardless of the triggering mechanism for ectopic calcification (e.g., loss of calcification inhibitors, accumulated protein aggregates, inflammation, phenotypic osteogenic cellular transformation, or disordered mineral metabolism), the final common pathway of HAP aggregation creates the growing calcium crystal structure.

The active ingredient of SNF472 is IP6, a natural substance found in beans, brown rice, corn, sesame seeds, wheat bran, and other high-fiber content foods. In mammalian tissues intracellular concentrations of IP6 are much higher than extracellular concentrations. Intracellular IP6 is naturally present at the 10 to 100 µM level and is formed de novo from IP3 and the subsequent inositol polyphosphates family (IP4, IP5) (Grases et al, 2004; Perelló et al, 2004). Extracellular IP6 originates from dietary sources and reaches physiological levels in the 0.2 to 0.3 µM range (Grases et al, 2000). The calcium salt of IP6 is listed by the US Food and Drug Administration (FDA) as Generally Recognized as Safe. It is highly polar and poorly absorbed when given orally.

Based on current information, it is hypothesized that SNF472 is able to slow the process of vascular calcification by:

- Blocking the formation and growth of HAP crystals in the blood vessels. SNF472 is a polyphosphate with a high affinity for solid calcium salts. It quickly binds the surface of a forming nucleus or on the faces of a growing crystal and acts as an inhibitor of crystallization since it specifically binds to the growth sites (not the entire crystal surface), blocking the calcification process. An effect on the circulating colloidal calciprotein particles in the blood stream is also likely. SNF472 might be adsorbed on the surface of these nanoparticles, giving them negative charge and avoiding their aggregation to form the solid HAP crystal.
- Preventing the transformation of vascular smooth muscle cells (VSMC) to an osteogenic phenotype. Osteogenic mechanisms play a role in the development of CVC and cells derived from the vascular media undergo bone and cartilage-like phenotypic change and calcification in vitro under various conditions, including elevated calcium and phosphorous (Jono et al, 2000; Yang et al, 2004). SNF472 has been demonstrated to interfere in the molecular mechanisms that lead to the de-differentiation of VSMC to osteoblast-like cells (unpublished data on file, Sanifit).
- Reducing bone mass loss, which is a source of circulating calcium, especially relevant in patients receiving HD in whom there is an imbalance in the equilibrium of calcium between bone, blood, and soft tissues (Grases et al, 2010).

By stopping the progressive deposition of calcium within small arteriolar vessels, the principal pathological process underlying the development of the obliterative vasculopathy is halted. This is hypothesized to result in a reduction in pain and an improved ability for natural healing through neovascularization, white blood cell recruitment to fight infection, and a reduction in local inflammatory mediators.

1.3 SNF472 NONCLINICAL DATA

SNF472 has been extensively studied in nonclinical models for efficacy, safety, pharmacokinetics (PK), and toxicity, and showed a promising profile that supported progression to studies in humans. The results of nonclinical studies are summarized in the Investigator's Brochure.

In vitro and in vivo studies show that SNF472 inhibits calcification. In vivo studies show that SNF472 blocks the deposition of calcium (in the form of HAP crystallization) in heart and aorta tissue. A pharmacodynamic (PD) assay developed for use as a biomarker of SNF472 activity demonstrates that SNF472 reduces HAP crystallization in plasma, thus likely preventing further growth and progression of calcification in soft tissue and the vasculature. The initial validation of the PD assay was conducted in human and rat plasma (Ferrer et al, 2017), in which the addition of SNF472 to plasma samples in vitro or in vivo reduced the HAP crystallization rate. Subcutaneous administration of SNF472 in rats reduced the HAP crystallization potential of plasma up to 70%. Importantly, a correlation was shown between the PD assay results and vascular tissue calcification using the in vivo vitamin D model.

Nonclinical safety, reprotoxicology, and toxicology work has been completed, including studies of up to 6 months in rats and 9 months repeated-dose toxicology in dogs. No observed adverse effect levels obtained in these studies establish a wide safety margin that provides appropriate toxicology support to proceed to clinical studies.

Importantly, SNF472 did not significantly inhibit or bind to ion channels and transporters responsible for cardiac function, such as the human ether-a-go-go (hERG) channel. Therefore, SNF472 is not expected to have any direct effect on cardiac function in humans.

In vitro, SNF472 did not inhibit relevant human efflux transporters; uptake transporters; human cytochrome p450 (CYP)1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4; and did not induce human CYP1A2, CYP2B6, and CYP3A4. Therefore, clinically relevant drug-drug interactions are not anticipated with SNF472 in humans.

1.4 CLINICAL EXPERIENCE

Two Phase 1 studies of SNF472 have been completed: SNFCT2012-03 in healthy volunteers and subjects receiving HD and SNFCT2014-03 in subjects with ESRD receiving HD. Two Phase 2 studies have been completed: SNFCT2015-04 in subjects with CUA and SNFCT2015-05, to assess the effect of SNF472 on progression of CVC in addition to standard of care in approximately 270 subjects with ESRD receiving HD.

1.4.1 Pharmacokinetic and Pharmacodynamic Results

In the two Phase 1 studies (SNFCT2012-03 and SNFCT2014-03), PK parameters were similar between healthy volunteers and subjects receiving HD, indicating that HD therapy has little influence on the PK of SNF472. In both studies, the maximum observed concentration (C_{max}) of SNF472 occurred immediately following the end of the infusion, after which concentrations declined rapidly to below the limit of quantification (BLQ) within approximately 6 to 8 hours. The mean half-life ($t_{1/2}$) in these studies was between approximately 30 and 60 minutes.

No accumulation of SNF472 over time was observed in either Phase 2 study. In SNFCT2015-04 (SNF472 doses of 5.6 - 8.6 mg/kg TIW) the C_{max} of SNF472 was similar at Weeks 1 and 12. In SNFCT2015-05 (SNF472 doses of 300 mg or 600 mg TIW) the C_{max} of SNF472 was similar within dose groups at Weeks 1 and 52.

Mean inhibitions of ex vivo HAP crystallization (PD assay) up to approximately 80% were observed in the Phase 1 studies and up to 65-75% in the Phase 2 studies. Dose-PD relationship analysis using the human HD patient plasma samples showed that SNF472 inhibited systemic blood calcification with an IC_{50} of 2.2 mg/kg and IC_{80} of >5.6 mg/kg.

1.4.2 SNFCT2015-04, a Phase 2 Study in CUA

SNFCT2015-04 was a Phase 2 open-label, single-arm, repeat-dose study which examined the effect of SNF472 in addition to background care on wound healing and other parameters of therapeutic response in 14 subjects with CUA (Brandenburg et al 2019). SNF472 was administered at 3 HD sessions per week for 12 consecutive weeks. SNF472 (400 to 900 mg) was dosed according to body weight category, resulting in doses ranging from 5.6 to 8.6 mg/kg, administered by a constant infusion during the dialysis session of approximately 2.5 to 3 hours in duration.

Wound healing, pain, and quality of life (QoL) were assessed using the Bates-Jensen Wound Assessment Tool (BWAT), independent qualitative review of wound images, the Pain Visual Analog Scale (VAS), and the Wound-QoL questionnaire. BWAT total is a standardized tool for quantitative assessment of wound healing which rates wounds according to these 13 items: size, depth, edges, undermining, necrotic tissue type, necrotic tissue amount, exudate type, exudate amount, surrounding skin color, peripheral tissue edema, peripheral tissue induration, granulation tissue, and epithelialization.

Consistent improvement was observed across all of these measures. A statistically significant improvement from baseline in wound healing of the primary lesion was observed at Weeks 10 and 12 as measured by the BWAT total. The mean decrease from baseline in BWAT total score at Week 12 was 8.1 ($p<0.001$). Independent review of wound images closely followed the BWAT scores with the same trend in improvement observed in most subjects. In addition, reductions in Pain VAS were observed starting from Week 6. The mean decrease from baseline in Pain VAS at Week 12 was 23.6 mm ($p=0.015$). Improvements in the Wound-QoL questionnaire global score were observed with a mean decrease from baseline at Week 12 of 0.9 units ($p=0.003$).

In a post-hoc analysis, a targeted modification of the BWAT, the “BWAT-CUA” was developed with input from an interdisciplinary group of experts in calciphylaxis and wound care. The

BWAT-CUA items focus on the most clinically relevant features of CUA lesions: necrotic tissue type, necrotic tissue amount, exudate type, exudate amount, skin color surrounding wound, peripheral tissue edema, peripheral tissue induration, and granulation tissue. Each item was scored on a scale of 1 to 5 with a range of possible scores from 8 to 40. Mean (SE) BWAT-CUA improved from 21.2 ±2.0 at baseline to 14.9 ±1.4 at Week 12 ($p<0.002$; Sinha et al, 2018).

1.4.3 SNFCT2015-05, A Phase 2 Study Evaluating Safety and Efficacy on Progression of CVC

SNFCT2015-05 (CaLIPSO) is a completed Phase 2b, randomized, double-blind, placebo-controlled study that assessed the effect of 2 dose levels of SNF472 (300 mg and 600 mg) on progression of CVC when added to standard care in subjects with ESKD on HD (Raggi 2020). A total of 273 subjects received at least 1 dose of study drug: SNF472 300 mg (n=92), SNF472 600 mg (n=91), or placebo (n=90) administered by intravenous (IV) infusion TIW during dialysis for 52 weeks. The primary endpoint was change in coronary artery calcium (CAC) volume score from baseline to Week 52 as measured by CT scan. In the modified Intent to Treat (ITT) population, SNF472 significantly reduced the progression of CAC compared with placebo: the mean change in CAC volume score was 11% (95% confidence interval [CI], 7% to 15%) in the SNF472 combined dosing group compared with 20% (95% CI, 14% to 26%) in the placebo group ($p=0.016$ vs SNF472). Additionally, SNF472 significantly reduced the progression of calcium volume score relative to placebo in the aortic valve (14% [95% CI: 5% to 24%] versus 98% [95% CI: 77% to 123%]; $p<0.001$) but not in the thoracic aorta (23% [95% CI: 16% to 30%] versus 28% [95% CI, 19–38]; $p=0.40$).

1.4.4 Safety and Tolerability Results with SNF472

SNF472 has been well tolerated in clinical studies to date.

In Study SNFCT2012-03 (N=28), the majority of non-serious adverse events (AEs) observed in healthy volunteers were infusion site-related events that were considered to be related to SNF472 by the Investigator. In HD subjects, similar infusion site-related adverse events were not observed as SNF472 was infused through the dialysis circuit with dilution in blood before reaching the subject's blood vessels. There were mild to moderate AEs reported in the multiple ascending dose Study SNFCT2014-03 but none were considered related to SNF472.

In the open-label Phase 2 CUA Study SNFCT2015-04 (N=14), AEs reported in more than one subject were cellulitis, diarrhea, prolonged QT interval, fluid overload, hypertension, hypoesthesia, nausea, and skin lesion (n=2 each); all other AEs were reported in 1 subject. Most of the AEs were mild to moderate in intensity.

In Study SNFCT2015-05 (CaLIPSO), the most common treatment-emergent AEs for which subject incidences were higher in the combined SNF472 treatment group than in the placebo group by a difference of at least 2% were abdominal pain upper (7.1% vs 2.2%), atrial fibrillation (6.6% vs 2.2%), hypoglycemia (6.6% vs 1.1%), hyperkalemia (6.0% vs 3.3%), and hyperphosphatemia (3.8% vs 0%). All subjects in this study with AEs of hypoglycemia had a history of diabetes, most AEs of hypoglycemia were mild to moderate, all but one were

considered not related to study drug, and all resolved. The AEs of hyperkalemia and hyperphosphatemia were expected in subjects on HD.

Serious AEs (SAEs) were reported by 1 subject (polycystic kidney infection) in the Phase 1 Study SNFCT2014-03 (N=18) and by 7 subjects in the Phase 2 Study SNFCT2015-04. The SAEs reported in Study SNFCT2015-04 were abdominal wound dehiscence, cardiogenic shock, cellulitis, dry gangrene, fluid overload, gangrene, hematemesis, hypertensive emergency, nausea, pulmonary edema, renal failure, sepsis, and urinary tract infection, n=1 for each. Most of the SAEs are commonly seen in this patient population. None of the SAEs reported in either study were considered related to SNF472 by the Investigator. In Study SNFCT2015-05, the most commonly reported SAE was renal transplant which was similar between combined SNF472 dose group and placebo (10.9% vs. 10.0%). Renal transplants are expected in this population and meet SAE criteria (hospitalization) but are not considered a negative outcome in this population. The other SAE that was reported for more than 5% of subjects overall was pneumonia (3.8% in the combined dose groups and 7.8% in the placebo group). The following SAEs were reported for no subjects in the placebo group and >3% of subjects in the SNF472 600 mg group: cardiac arrest (4 subjects), gastrointestinal hemorrhage (3 subjects), atrial flutter (3 subjects), and pyrexia (3 subjects).

Two deaths were reported during the Phase 2 Study SNFCT2015-04; neither death (1 due to cardiogenic shock and 1 due to cardiopulmonary arrest subsequent to withdrawal from hemodialysis) was considered related to SNF472 by the Investigator. In Study SNFCT2015-05, death occurred in 7 subjects (4%) who received SNF472 and 5 subjects (6%) who received placebo; 2 of the deaths were cardiovascular (cardiac arrest in the 600 mg group and cardiac failure congestive in the placebo group); none were considered by the Investigator to be related to study drug.

Overall, in clinical studies no clinically significant effects were reported in vital signs or laboratory values, including hypocalcemia. In the open-label study (SNFCT2015-04), there were 2 TEAEs of QT prolongation and 1 of tachycardia. One TEAE of QT prolongation was considered not related. The other event of QT prolongation occurred 7 days after SNF472 infusion but was considered possibly related by the Investigator, and the event of tachycardia was considered possibly related by the Investigator. In the placebo-controlled study (SNFCT2015-05) incidence of tachycardia was similar between SNF472 600 mg (4.4%) and placebo (3.3%); none of the tachycardia TEAEs were considered related by the Investigator. There was 1 TEAE of QT prolongation reported in the SNF472 300 mg group (1.1%) in SNFCT2015-05 and considered possibly related by the Investigator.

Based on the totality of nonclinical and clinical data generated to date, no clinically relevant safety risks have been identified that preclude continued human investigation with SNF472.

Refer to the Investigator's Brochure for additional details.

1.5 RATIONALE FOR THE STUDY

Calciphylaxis is a life-threatening disease with a high mortality rate that mainly occurs in patients with ESRD receiving dialysis (Section 1.1.1). As there are no approved therapies for CUA (Section 1.1.2), there is an unmet need to improve the course of wounds and, ultimately, to improve CUA-related outcomes for patients. Thus, this Phase 3, double-blind, randomized, placebo-controlled study is designed to assess the efficacy and safety of SNF472 when added to background care for the treatment of CUA in subjects with ESRD receiving HD. The study hypothesis is that administration of SNF472 in addition to background care over 12 weeks will improve wound healing, pain, and wound-related QoL compared to placebo.

1.6 RISK-BENEFIT ASSESSMENT

Potential Benefits of Study Participation

Benefits to individual subjects may include:

- Receipt of a potentially efficacious treatment for calciphylaxis
- Intensive monitoring of calciphylaxis wounds that may be more thorough and frequent than usually received through standard care outside of a clinical trial
- Contribution to the development of a treatment for patients suffering from calciphylaxis

Subjects treated with placebo during Part 1 of the study will receive SNF472 during Part 2. During Part 1, placebo-treated subjects may benefit from the closer follow-up and will continue to receive calciphylaxis background care.

Risks from Study Participation

In nonclinical studies, transient hypocalcemia associated with some degree of QT prolongation was induced with rapid infusion of high concentration SNF472 but was not induced when the same concentration was administered via a slow infusion over 2 hours. Hypocalcemia and associated QT prolongation are not expected in dialysis patients since a dilute solution of SNF472 is infused slowly into the dialysis circuit with constant exposure to a standard calcium concentration gradient across the dialysis membrane. Indeed, no clinically significant trends in hypocalcemia or QT prolongation have been observed in either of the Phase 2 studies (SNFCT2015-04 and SNFCT2015-05). Those studies used comparable doses of SNF472 as in this study. Monitoring for changes in calcium and heart rhythm in the current study include pre- and post-dose collection of blood samples for measuring ionized calcium levels, pre- and post-dose 12-lead ECGs, and continuous Holter monitoring over a 4-4.5 hour window including the time of study drug infusion.

Safety monitoring procedures described in the protocol are considered to be adequate to protect subject safety. In addition, an independent Data and Safety Monitoring Board (DSMB) will perform regular, periodic assessments of blinded and unblinded data to detect any potential safety signals that may arise during the study and will advise the sponsor accordingly.

COVID-19 Management

During the global SARS-CoV-2 pandemic and without appropriate social distancing and personal protective equipment, there is a potential for increased exposure to SARS-CoV-2. Subjects are required to attend healthcare facilities for their hemodialysis sessions three times in a week during which they will receive study drug and undergo all study procedures. No separate or additional visits outside of the subjects' hemodialysis sessions are expected. Clinical sites are to follow their SARS-CoV-2 procedures and local guidelines to ensure an appropriate COVID-19 prevention and protection strategy.

Overall Benefit/Risk Conclusion

Calciphylaxis is a life-threatening disease with a high mortality rate that mainly occurs in patients with ESRD receiving dialysis. As there are no approved therapies for calciphylaxis, there is an unmet need to improve the course of wounds and, ultimately, to improve calciphylaxis-related outcomes for patients. The totality of nonclinical and clinical data generated to date, including data from a 52-week placebo-controlled Phase 2 study (SNFCT2015-05), support a favorable benefit/risk profile for the study of SNF472 in this calciphylaxis population. Potential for additional risks will be monitored over the course of the trial and in the SNF472 clinical development program more broadly.

More detailed information about the efficacy and safety profile of SNF472 is provided in the Investigator's Brochure.

2 STUDY OBJECTIVES

The objectives of this study are:

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

3 STUDY DESIGN

3.1 STUDY DESIGN OVERVIEW

This Phase 3, global, multicenter study will include a screening period of up to 5 weeks (35 days), a 12-week double-blind, randomized, placebo-controlled period (Part 1) followed by a 12-week open-label treatment period (Part 2), and a 4-week follow-up period.

A study flow chart is provided in Figure 1.

Screening Period:

Informed consent will be obtained prior to performing any study procedures. Subject eligibility will be evaluated during the screening period, which will be conducted as a two-step process. In addition, the subject's pain medications should be stabilized between Screening Visit 1 and Screening Visit 2 to determine the baseline maintenance pain medication dose. Details of the screening process are provided in Section 5.1

In addition to pain medications, other aspects of the background care regimen (including wound care, dialysis parameters, other concomitant medications relevant to the management of CUA; Section 4.7.3) should be stabilized (or maintained if already stable) during the screening period.

Completion of screening within 4 weeks or less is preferred but up to 5 weeks is allowed.

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to receive either 7 mg/kg of SNF472 or matching placebo in a double-blind manner. Randomization will be stratified based on intravenous STS use at the time of randomization (yes/no).

Double-Blind, Randomized, Placebo-Controlled Treatment Period (Part 1): Subjects will receive SNF472 or placebo for 12 weeks in addition to background care (in accordance with the clinical practices of each site). No changes to the background care regimen, including pain medications, should be made after randomization unless medically indicated in the opinion of the Investigator.

The Schedule of Events for Screening Period and Part 1 is provided in Table 1.

Open-Label Treatment Period (Part 2): Subjects who complete Part 1 will be eligible to participate in Part 2, in which all subjects will receive open-label SNF472 for 12 weeks and continue stable background care (in accordance with the clinical practices of each site), including pain medication, with no changes unless medically indicated in the opinion of the Investigator.

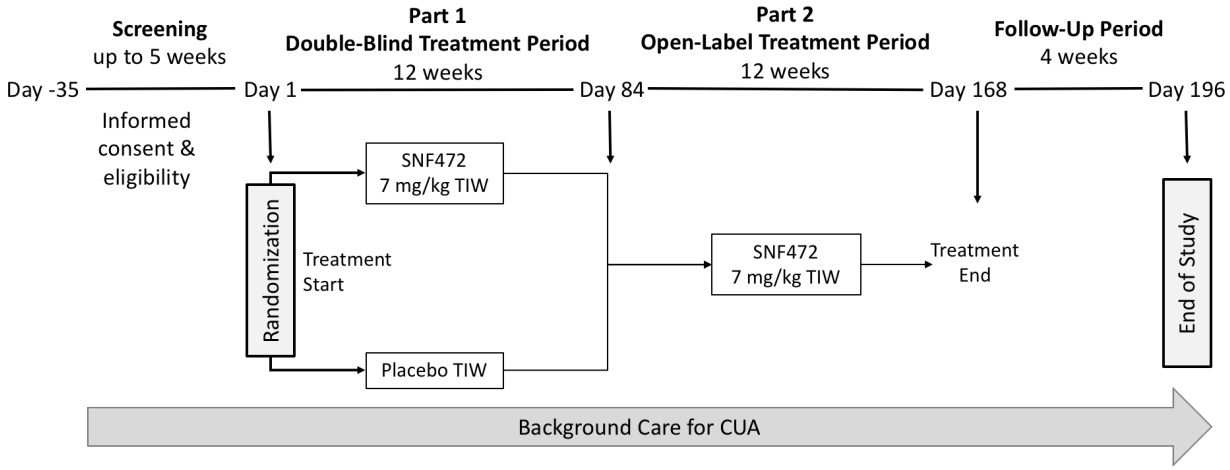
The Schedule of Events for Part 2 and the follow-up visit is provided in Table 2.

Follow-Up Period/ Early Termination: Subjects completing the study will return for a follow-up visit 4 weeks after the last dose of study drug. Subjects should continue on stable background care during the 4-week follow-up period, including pain medication, with no changes unless medically indicated in the opinion of the Investigator. Subjects who discontinue study drug during Part 1 or Part 2 will be asked to complete study assessments throughout the respective part of the study (Part 1 or Part 2) and complete the follow-up visit. Subjects who discontinue study drug and are unwilling to complete the remaining study assessments will be encouraged to return for an early termination visit 4 weeks after the last dose of study drug.

A subject is considered to have completed the study if the subject has completed all study visits, including the final follow-up visit.

The end of the study is defined as the date of the last study visit of the last subject in the study.

Figure 1. Study Design Flowchart



TIW = 3 times weekly

3.2 DISCUSSION OF STUDY DESIGN

This Phase 3 study has been designed to assess the efficacy and safety of SNF472 for the treatment of CUA. Part 1 of the study will be conducted in a randomized, double-blind, placebo-controlled manner. All subjects will receive SNF472 in Part 2, giving subjects who received placebo in Part 1 the opportunity to receive the active treatment, and generating a total of up to 24 weeks of safety and efficacy data in those subjects who received SNF472 in Part 1.

The control therapy will be a matching placebo, rather than an active comparator, because there are currently no approved medicinal products or devices for the treatment of this disease. Subjects in both treatment groups should receive background care for CUA in accordance with the clinical practices at each site, and this treatment should continue for the duration of the study, including during the follow-up period. Current background care usually includes 1) reducing clinical factors that may exacerbate the deposition of calcium in vascular tissue, 2) wound care, and 3) control of pain (Goel et al, 2011; Seethapathy et al, 2019), and is described further in Section 1.1.2.

The efficacy of SNF472 will be assessed using clinically meaningful quantitative endpoints of wound healing assessed by BWAT, pain assessed by VAS, and quality of life assessed with the wound-related QoL questionnaire. These endpoint assessments are described further in Section 5.6 and Section 3.3. Safety will be evaluated including assessment of AEs, laboratory parameters, 12-lead ECGs, Holter monitoring, and vital signs.

The 12-week duration of Part 1 was selected as appropriate for assessment of the primary and secondary efficacy endpoints based upon data from the Phase 2 CUA Study SNFCT2015-04. As summarized in Section 1.4.2, clinically and statistically significant improvements in wound healing, pain, and quality of life were observed following 12 weeks of SNF472 treatment in that study.

The second part of the study (Part 2) will be a 12-week open-label treatment period in which all subjects will receive SNF472. Thus, maximum exposure to SNF472 will be up to 24 weeks.

Diagnosis of CUA will be made by the Investigator. A central wound rating group will review wound images to confirm the primary lesion is due to CUA. No consensus has been established as to whether confirmation by biopsy is necessary for diagnosis of CUA and some experts believe it has a risk of inducing new lesions and infectious complications (Brandenburg et al 2016). Therefore, confirmation of CUA diagnosis by skin biopsy is not required for inclusion in this trial. While evidence of arteriolar calcification from biopsy is supportive of a CUA diagnosis its absence does not rule out CUA as findings are highly dependent upon sample quality and the location from which it is obtained. However, biopsies may be performed based on Investigator decision.

3.3 APPROPRIATENESS OF ASSESSMENTS

The primary and secondary efficacy assessments in this study (BWAT-CUA, Pain VAS, Wound-QoL, and BWAT total) are well-characterized, as described below. BWAT total, Pain VAS, and Wound-QoL were pre-specified endpoint measures in the Phase 2 study of SNF472 for the treatment of CUA (SNFCT2015-04).

BWAT total and subsets of the BWAT have been widely used for measuring and predicting wound healing in clinical settings and have been used successfully in clinical studies of chronic wounds, including pressure ulcers, diabetic ulcers, and venous leg ulcers (e.g., Bellingeri et al, 2016; Chan and Lai, 2014; Gupta et al, 2009). Content validity, concurrent validity, predictive validity, intra-rater reliability, and inter-rater reliability of the BWAT total have been well documented (Cauble, 2010; Bates-Jensen and Sussman 2011). The BWAT-CUA is a modification of BWAT which focuses on the prototypical features of CUA lesions and was developed with reference to the Phase 2 results. The BWAT-CUA was selected as a primary efficacy measure for Phase 3 to provide an objective, quantitative CUA-focused tool that can be applied systematically across study sites to assess changes in CUA lesions over time.

Both BWAT-CUA and BWAT total showed statistically significant improvements in wound healing from baseline to Week 12 with SNF472 (Section 1.4.2) in the Phase 2 study, demonstrating their suitability for evaluating improvement in wound healing over time in subjects with CUA. A correlation between improvement in BWAT total and Pain VAS was also demonstrated in that study.

The Pain VAS, a well-characterized self-assessment tool, has been shown to be a reliable method for measurement of pain intensity and responses to pain treatment (Hawker et al, 2011; Katz and Melzack, 1999; Swanson, 2014).

The Wound-QoL questionnaire is a validated self-assessment tool that has been shown to be feasible for assessing health-related QoL in patients with chronic wounds (Augustin et al, 2014; Blome et al, 2014).

3.4 STUDY POPULATION

Planned enrollment is approximately 66 subjects from approximately 60 sites in multiple countries. Number of subjects may be adjusted up to a maximum of 99 based on results of a sample size re-estimation (SSRE).

3.4.1 Inclusion Criteria

Subjects meeting all of the following criteria will be considered for enrollment in the study:

1. ≥18 years of age
2. Receiving maintenance HD in a clinical setting for at least 2 weeks prior to screening
3. Clinical diagnosis of CUA by the Investigator including ≥1 CUA lesion with ulceration of the epithelial surface. A central wound rating group will review wound images to confirm the primary lesion is due to CUA.
4. CUA wound-related pain shown by a Pain VAS score ≥50 out of 100
5. Primary lesion that can be clearly photographed for the purpose of protocol-specified wound healing assessments
6. Willing and able to understand and sign the informed consent form (ICF) and willing to comply with all aspects of the protocol

3.4.2 Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Subjects whose primary lesion is due to causes other than CUA
2. History of treatment with bisphosphonates within 3 months of baseline (Week 1 Day 1)
3. Severely ill subjects without a reasonable expectation of survival for at least 6 months based on the assessment of the Investigator
4. Subjects with a scheduled parathyroidectomy during the study period
5. Expectation for kidney transplant within the next 6 months based on Investigator assessment or identification of a known living donor
6. Pregnant or trying to become pregnant, currently breastfeeding, or of childbearing potential (including perimenopausal women who have had a menstrual period within one year) and not willing to either completely avoid sexual intercourse with a person of the opposite sex or use a highly effective method of birth control (specified in Section 4.7.4.2) from screening through at least 30 days after last dose of study drug
7. Significant noncompliance with dialysis treatment evidenced by repeated missed dialysis sessions (including if due to hospitalizations where dialysis treatment is unavailable) or significant noncompliance with medication regimen, in the judgment of the Investigator
8. Any history of active malignancy within the last year (history of localized basal cell or squamous cell carcinoma that has been excised/appropriately treated or a fully excised malignant lesion with a low probability of recurrence will not be considered exclusionary)

9. Clinically significant illness other than CUA within 30 days prior to screening that in the judgment of the Investigator could interfere with interpretation of study results, impair compliance with study procedures, or impact the safety of the subject (e.g., unstable angina, unstable heart failure, stroke, uncontrolled hypertension, or other illness requiring hospitalization)
10. Participation in an investigational study and receipt of an investigational drug or investigational use of a licensed drug (with the exception of intravenous STS) within 30 days prior to screening. If participating in an investigational study of intravenous STS, all visits of that study must be completed prior to screening for this study. *Note: Off-label use of intravenous STS outside of an investigational study is not restricted.*
11. Past or current participation in another clinical study with SNF472
12. History or presence of active alcoholism or drug abuse as determined by the Investigator within 6 months before screening or concurrent social conditions that, in the opinion of the Investigator, would potentially interfere with the subject's study compliance
13. Mental impairment or history of or current significant psychiatric disease that, in the opinion of the Investigator, may impair ability to provide informed consent or impact compliance with study procedures
14. Any other condition or circumstance that, in the opinion of the Investigator, may make the subject unlikely to complete the study or comply with study procedures and requirements, or may pose a risk to the subject's safety and well-being
15. Subjects whose CUA lesions exhibit significant improvement, in the opinion of the Investigator, between the first and second screening visit

4 STUDY TREATMENTS

4.1 STUDY DRUGS

Description of the study drugs are provided in Table 3.

Table 3. Identity of the Study Drugs

	Active Treatment	Matching Placebo (Part 1 only)
Code name	SNF472	Not applicable
Description	Clear, colorless solution free from visible particles	Clear, colorless solution free from visible particles
Composition	SNF472, 30 mg per 1 mL of physiological saline (0.9% sodium chloride)	Physiological saline (0.9% sodium chloride)
Dosage form	Solution for IV infusion	Solution for IV infusion
Strength	30 mL sterile vials containing 30 mg/mL (900 mg/vial)	Identical 30 mL sterile vials containing physiological saline
Dose (based on body weight)	7 mg/kg	none

IV=intravenous

Each kit will be given a unique code number, traceable to the batch number of the study drugs.

4.2 DOSE RATIONALE

The dose of SNF472 for this study is 7 mg/kg, to be administered 3 times weekly (TIW) over approximately 2.5 – 3 hours at dialysis sessions during the 2 treatment periods. This dose was selected based on the results from the Phase 2 study in CUA (Brandenburg et al, 2018) and supported by nonclinical toxicology and PK studies along with PK and PD results from the Phase 1 and 2 clinical studies (SNFCT2012-03, SNFCT2014-03, and SNFCT2015-04).

Nonclinical data have shown that SNF472 is a potent and selective calcification inhibitor in vitro, in vivo, and in a biomarker assay that estimates PD activity by measuring inhibition of HAP crystallization (Ferrer et al, 2017; Section 1.3). Efficacy of SNF472 was demonstrated between 2 and 10 µM in animal models, with a very steep dose-response relationship and a narrow range between initial evidence of efficacy and asymptotic maximal efficacy.

The two Phase 1 clinical Studies SNFCT2012-03 and SNFCT2014-03 evaluated single-dose and multiple-dose administration in subjects receiving HD (Section 1.4). The single dose studied was 9 mg/kg (720 mg/day for an 80-kg subject) and the multiple doses ranged from 1 to 20 mg/kg TIW for 1 week (up to 1600 mg/day for an 80-kg subject) and 10 mg/kg (800 mg/day for an 80-kg subject) TIW for 1 month. The C_{max} of SNF472 for the 20 mg/kg dose was 101 µM at Day 1 and 85 µM at Day 5, and showed no accumulation after repeat TIW dosing, consistent with the short SNF472 $t_{1/2}$ of approximately 30 to 60 minutes (Section 1.4.1).

The dose used in the Phase 2 CUA Study SNFCT2015-04 was based on PK/PD and dose-PD relationships using a single direct-effect model based on the Hill approach (Goutelle et al, 2008) or a sigmoid E_{max} model, using the systemic exposure (C_{max} and AUC) and doses, respectively, from the Phase 1 Study SNFCT2014-03. The dose of SNF472 administered at each session was 400-900 mg, based on body weight categories designed to have all subjects with an administered dose close to 7 mg/kg. The actual range of doses administered was 5.6-8.6 mg/kg.

The mean (± standard deviation [SD]) C_{max} in Study SNFCT2015-04 was 29.1 ± 19.1 µM and 28.1 ± 21.0 µM at Weeks 1 and 12, respectively. The mean (± SD) PD effect was 65% ± 14 % and 60% ± 29% inhibition at Weeks 1 and 12, respectively. No dose-PD correlation was apparent because the lowest dose of 5.6 mg/kg provided a maximal PD response, and higher doses were within the plateau of the PD response observed in the previous clinical studies.

The dose of 7 mg/kg (e.g., 560 mg/day in an 80-kg subject) was selected for this Phase 3 study based on the following considerations:

- This dose is expected to provide maximal inhibition of calcification based on dose-PD analyses from the Phase 1 and Phase 2 studies.
- The pharmacological response shows a very narrow window between no activity and maximal activity.
- There is no accumulation of the compound after repeat TIW dosing; therefore, estimations of plasma concentrations expected for certain doses performed from 1- and 3-month clinical studies should also apply for a treatment duration of 6 months.

- SNF472 will be administered via IV infusion directly into the dialysis tubing, the same method used in the Phase 2 CUA Study SNFCT2015-04.
- This dose provides adequate safety margins of systemic exposure in toxicology studies conducted in nonclinical species.

4.3 TREATMENT ASSIGNMENT

Eligible subjects will be randomized in a 1:1 manner to either 7 mg/kg SNF472 or placebo. Randomization will be stratified based on intravenous STS use (yes/no) at the time of randomization.

Randomization will occur at Screening Visit 2 which may occur up to one week prior to the start of dosing on Week 1 Day 1 and will be performed using a centralized electronic randomization system that is part of the Interactive Response Technology (IRT).

In Part 2, all subjects will receive open-label 7 mg/kg SNF472.

4.4 BLINDING, PACKAGING, AND LABELING

4.4.1 Blinding

Part 1 will be performed in a double-blind manner. Part 2 will be open label. The Investigator, site staff, subjects, and Sponsor staff (including designees) involved in the conduct of the study and data management will remain blinded to the treatment assignment for Part 1 for the duration of the study including Part 2 and follow-up until the study database is locked, except as described in Section 4.4.2.

To maintain the blinded nature of Part 1 of the study, the SNF472 and matching placebo treatments will be identical in appearance, and the volume of solution administered to subjects in both treatment groups will be based on body weight.

4.4.2 Unblinding

The study blind for Part 1 should not be broken except in a medical emergency (where knowledge of the study drug administered would affect the treatment of the emergency) or regulatory requirement (e.g., for SAEs).

The decision to break the blind can only be made by the Investigator, or other persons duly registered in the clinical trial file as sub-Investigators. If possible, the Investigator should consult with the Medical Monitor prior to breaking the blind. Unblinded staff members will not convey information regarding treatment assignments in the study, whether informally or formally, to any other person, unless required for medical reasons. If the blind is broken, the date, time, and reason must be recorded and included in any associated AE report.

If an emergency unblinding becomes necessary, the Investigator should request the unblinding information through the centralized electronic randomization system and notify the Sponsor/Medical Monitor of the unblinding.

The ethics committee should be informed if a subject's treatment is unblinded at the site level. After the unblinding the Investigator shall determine if the subject is to continue or discontinue study drug. The Investigator's decision should be based on the risk to benefit determination for the subject and should be discussed with the medical monitor prior to implementing the decision when possible. The Sponsor should be informed of the decision.

4.4.3 Packaging, Labelling, and Storage

The study drugs will be labelled according to the applicable local health authority and/or regulatory requirements. Study drugs will be sent to the central or local depots and the depots will then send the study drugs to the study site. Study drug shipments will be under refrigerated conditions.

All supplies of study drug must be stored under refrigeration at the sites. The Sponsor should be notified of any significant study drug temperature excursions.

4.5 ADMINISTRATION OF STUDY DRUG

Preparation of study drug for administration will be done by trained and qualified technicians or pharmacists. Detailed instructions on preparation of the study drug for administration will be provided in the Pharmacy Manual.

The study drug should be administered TIW in conjunction with the subject's dialysis sessions. If subjects have dialysis sessions more than 3 times per week, the study drug will only be administered TIW according to the schedule of events outlined in Table 1 and Table 2.

In Part 1, the dose of blinded study drug will be based on the subject's body weight recorded after hemodialysis during screening. In Part 2, the dose of SNF472 will be based on the subject's body weight recorded after hemodialysis at Week 12, Day 5 of Part 1.

The appropriate volume of the study drug will be removed from the vial and then diluted in physiological saline and administered as a constant rate IV infusion with an infusion pump connected directly to the dialysis machine **before** the dialyzer via an IV infusion set, as shown in Figure 2. The preparation of study drug and the infusion procedure will be described in the Pharmacy Manual. The study drug should **NOT** be administered by bolus or directly into the vein. The study drug should **ALWAYS** be administered via the dialysis tubing before the dialyzer.

The infusion should begin just after the start of the HD procedure and should be administered over a period of approximately 2.5 – 3 hours. The total dose should be delivered at each dosing session, even in the event of infusion interruptions that may extend the dosing duration.

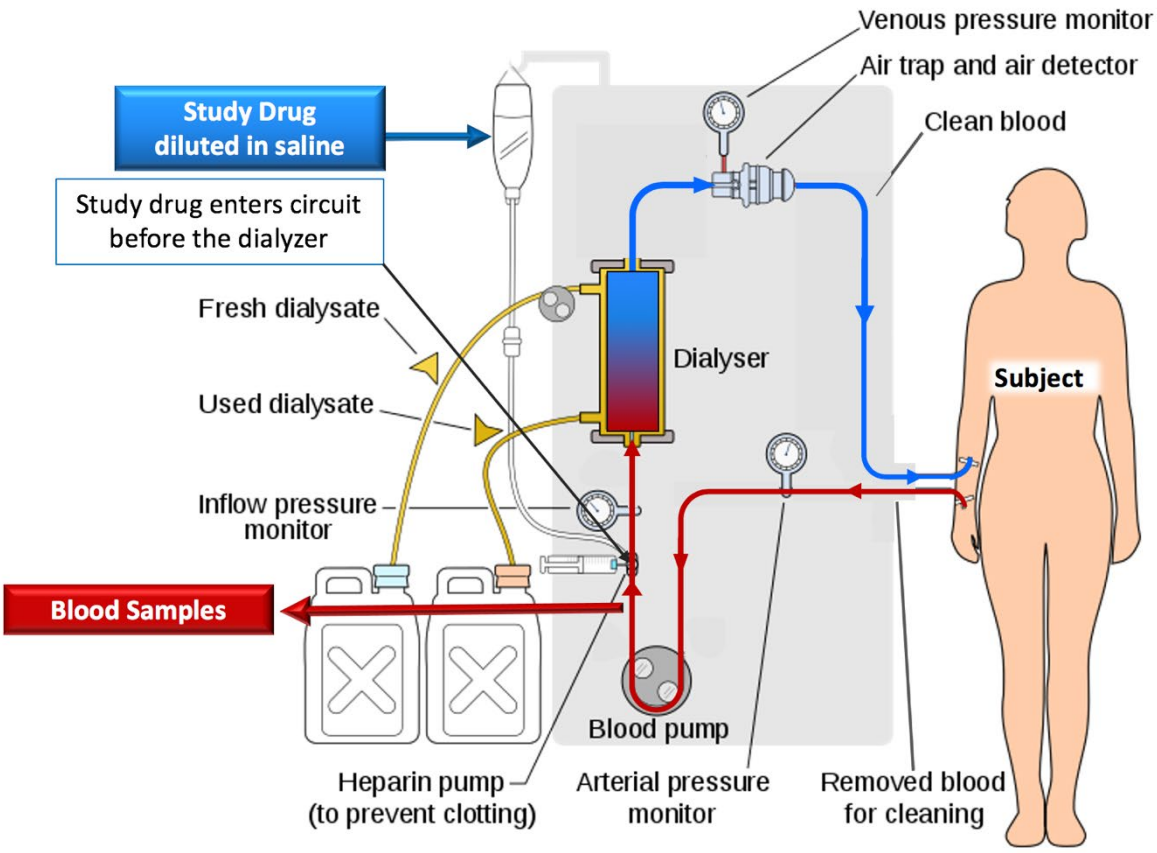
No direct interactions are expected between SNF472 and STS, however no studies have been conducted to evaluate administration of the two drugs together, thus SNF472 should NOT be administered concomitantly with STS. In the event that both drugs need to be administered to the subject, the administration of STS should occur after administration of SNF472 during the last 30 minutes of the HD session.

Investigators should consider whether any changes to the dialysis prescription will be needed to account for the volume of saline used for delivery of the study drug and track the weight of

subjects after hemodialysis (as per usual practice), adjusting dialysis settings if needed for maintaining volume balance.

For each study drug infusion, the site will document the actual start and stop times of the infusion, the total volume infused, and any interruption and resumption of the infusion along with the reason for the interruption.

Figure 2. Method of Study Drug Administration



Note: SNF472 is not removed by dialysis and the diluted study drug should be added to the dialysis line *before the dialyzer*.

4.6 SUPPLIES AND ACCOUNTABILITY

The Investigator or designee is responsible for maintaining accurate accountability records of the study drug vials throughout the clinical study.

Cumulative inventory and dispensing of study drug will be recorded throughout the study using the centralized electronic system and electronic data capture (EDC).

All sites will return unused study drug vials to the depot. Broken or damaged vials will be destroyed on-site following the site's Drug Destruction Policy and accounted for within the drug accountability records. The unused study drug return for destruction will only occur after drug accountability has been performed, after any discrepancies have been resolved, and after receiving approval of destruction by the Sponsor or designee.

4.7 PRIOR AND CONCOMITANT MEDICATIONS, BACKGROUND CARE FOR CUA, WOUND CARE, DIALYSIS PARAMETERS, AND LIFESTYLE RESTRICTIONS

4.7.1 Prohibited Concomitant Medications

- Bisphosphonates should not be used within 3 months prior to baseline (Week 1 Day 1) or at any time throughout the study.
- Intralesional STS treatment of the wound should not be used from the time of randomization or at any time throughout the study.

4.7.2 All Prior and Concomitant Medications

The use of any other treatments or medications considered necessary by the Investigator for management of the subject's health and medical condition are allowed during this study.

At screening, medications taken during the past 30 days will be recorded as prior medications in the eCRF (including dose, duration, and reason for administration).

New medications and/or changes in ongoing prior medications relative to screening will be documented before the first dose of study drug on Week 1 Day 1.

After the first dose of study drug, new medications and/or changes to ongoing medications, including pain medications, will be recorded as concomitant medications in the eCRF with details including but not limited to dose, duration, and reason for administration according to the schedule in Table 1 and Table 2.

4.7.3 Background Care for CUA

All subjects should receive background care for CUA in accordance with the clinical practices at each site. Background care includes wound care, dialysis parameters (calcium concentration in the dialysate, dialysis frequency and duration), pain medications, and other concomitant medications relevant to the management of CUA. A stable background care regimen should be established (or maintained if already in place) during the screening period and should continue throughout Parts 1 and 2 and the follow-up period. Additional information on stabilizing pain medications is provided in Section 4.7.3.1. After the screening period, no changes to the background care regimen, including the maintenance pain medication dose, should be made during the study unless medically indicated in the opinion of the Investigator.

Consideration should be given to potential triggers for CUA and Investigators should consider whether these measures are appropriate for their subjects: replacement of warfarin with another anticoagulant, withdrawal of calcium-based phosphate binders unless being used for

hypocalcemia, reduction in vitamin D administration, and a hemodialysis regimen of 4 hours, three times per week. Wounds should be monitored regularly for infection.

4.7.3.1 Stabilizing Pain Medications

The site staff should establish (or maintain if already in place) a stable pain medication regimen between Screening Visit 1 and Screening Visit 2.

At Screening Visit 1, the site staff will assess and record the details of all pain medications the subject is currently using to control pain for CUA and other reasons. Pain medications used for the prior 30 days will be included in the eCRF. The subject should be provided with a diary at Screening Visit 1 and instructed to record all use of pain medications (opioids and non-opioids) on a daily basis, indicating if the pain medication was for CUA lesion pain or pain from other causes. Subjects will be asked to record all pain medications they are currently taking and any newly prescribed pain medications taken during the screening period. Subjects should be instructed to bring the diary with them to the site at each visit. The site staff should review the diary with subjects at least weekly during the screening period and clarify, as needed, medications used, frequency, and dosage. Actual use from the diaries will be recorded by site staff in the eCRF. The Investigator or designee will evaluate pain medication stabilization beginning at Screening Visit 1 and on a weekly basis until Screening Visit 2.

The stable dose of pain medication used for CUA will be based on the subject's usage during a 7-day period prior to Screening Visit 2. A 2-week period of evaluation is suggested, but this duration may require less time or more time, up to three to four weeks, based on the needs of the subject. The week used for determining the stable dose should not be a week during which additional but short-term use of opioids was required during or due to medical procedures (e.g., surgical debridement, fistula procedures). If such additional opioid use occurred, the 7 days prior to the procedure or the 7 days after the procedure should be used to determine the stable dose. Note: Up to 5 weeks for screening is permitted, but the screening period may be shorter for some subjects.

When a stable dose has been determined, it be will be defined as the subject's maintenance dose for the remainder of the trial. The maintenance opioid dose will be calculated centrally as the average daily morphine milligram equivalents (MME) based on the information entered in the eCRF.

4.7.3.2 Maintenance of Pain Management During the Trial

Subjects will continue to record all pain medications taken in the diary on a daily basis throughout the trial and the site staff will continue to review the diary with subjects weekly and record actual pain medications used in the eCRFs.

Investigators should continue the prescriptions for pain medications established during the screening period as the baseline maintenance dose. If applicable, Investigators should coordinate with other providers involved in pain management for the subject and encourage them not to change pain medication unless medically indicated for worsening of pain control.

Also, Investigators should request the provider to inform them of any change in dose or addition of new pain medications.

The following general guidance for pain management during the study, based on pain severity, should be followed:

- Mild pain should be treated with acetaminophen and adjuvants such as pregabalin or gabapentin.
- If this combination is inadequate for pain control, addition of a low dose opiate such as oxycodone should be considered.
- Only if further pain control is required, use of higher doses and/or stronger opiates (e.g., fentanyl patch) should be considered, up to a maximally tolerated dose.
- If pain is not controlled despite this guidance, Investigators may follow regional or institution guidelines for management of pain.

4.7.3.3 CUA Wound Care

CUA wound care will be at the discretion of the treating physician but should avoid agents known to inhibit healing such as liquid povidone iodine and hydrogen peroxide. Surgical debridement may be considered, if necessary, to prevent systemic infection. Wound care received for CUA lesions will be recorded periodically according to the schedule in Table 1 and Table 2. CUA wound care recorded can include:

- Absorptive dressing (gauze, alginate)
- Impregnated, non-adherent gauze
- Gel dressing
- Cream/ointment therapy
- Enzymatic debridement
- Surgical debridement
- Negative pressure therapy
- Hyperbaric oxygen
- Other (specify)

4.7.3.4 Dialysis Parameters

Sites will be requested to record calcium concentration in the dialysate, the frequency and duration of dialysis, and record dialysis adequacy (Kt/V or URR) at each of the visits indicated in Table 1 and Table 2. Estimated values from the dialysis machine or calculated values using local lab measurements may be used. For each subject, the same measure of dialysis adequacy (Kt/V or URR) should be recorded at the visits indicated and it should be based on the same data source (dialysis machine or calculation using local labs) throughout the study.

4.7.4 Lifestyle Restrictions

4.7.4.1 Dietary Restrictions

No dietary restrictions are required for participation in this study. In addition, no restrictions on the timing of food or fluid intake with respect to dosing are required because the study drug administration will be IV.

4.7.4.2 Contraception Requirements

To prevent pregnancy, female subjects and female partners of male subjects, must not be of childbearing potential (i.e., menopausal for >1 year, surgically sterilized), must practice true abstinence, or must practice one of the highly effective contraceptive methods (i.e., results in <1% failure rate when used consistently and correctly) listed below from screening through 30 days after the last dose of study drug. True abstinence is defined as abstinence that is part of the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and declaration of abstinence for the duration of exposure to study drug are not acceptable. Withdrawal is also not an acceptable method of contraception.

- Female subjects of childbearing potential who are sexually active should use one of the following contraceptive methods:
    - Intrauterine device or intrauterine system in place for at least 3 months prior to first dose of study drug
    - Partner has had a vasectomy
        - Note: Vasectomy in the partner is only considered to be highly effective provided the partner is the sole sexual partner of the female subject of childbearing potential and the vasectomized partner has had a medical assessment of the surgical success.
    - Stable hormonal contraception associated with inhibition of ovulation (such as oral, transdermal, or depot regimen) for at least 3 months prior to first dose of study drug
    - Bilateral tubal ligation
- Male subjects who are sexually active and have a partner who is of childbearing potential should use a condom in addition to having their female partner use another acceptable method (see bullet point above) from screening through 30 days after the last dose of study drug.
    - Note: Male subjects must not have unprotected sexual intercourse with a female who is pregnant or breastfeeding during the study.

5 STUDY PROCEDURES AND ASSESSMENTS

5.1 SCREENING PERIOD

The schedule of assessments during the Screening Period is provided in Table 1.

Informed consent will be obtained prior to performing any study procedures. Screening will be conducted in two steps (Screening Visit 1 and Screening Visit 2).

Screening Visit 1:

At Screening Visit 1, the study staff should initiate the screening process by evaluating the inclusion/exclusion criteria, collecting the CUA lesion images (photographs and videos), demographic information (sex, age, race, ethnicity), prior/concomitant medications, including pain medication use, dialysis parameters, medical history, physical exam (including weight and height), and vital signs.

As the initial step during the screening process, the site personnel will complete and enter demographic information into the IRT system, acquire images of the subject's suspected CUA lesion(s) and will rate undermining, peripheral tissue edema, and peripheral tissue induration for these lesion(s). In addition, the site personnel will administer the Pain VAS pain and Wound QoL. The central wound rating group will confirm whether lesion(s) are due to CUA (according to details provided in the Central Wound Rating Charter). The subject should be provided with a pain medication diary and instructed to record on a daily basis all pain medications (opioids and non-opioids) taken and the reason the pain medications were taken (i.e., for CUA lesion pain or other non-CUA lesion pain).

Site personnel will be notified through the IRT system that the subject's lesion(s) and Pain VAS score have met eligibility requirements. Site staff can then continue to complete the remaining eligibility requirements (laboratory specimen collection, completion of medical history, and other evaluations).

During the subsequent week(s) prior to Screening Visit 2, the Investigator or designee should review the subject diary with the subject at least weekly, record actual pain medication use in the eCRF, and titrate the pain medications as needed (see Section 4.7.3.1 for additional details) until a stable pain medication regimen is achieved. When a stable dose is achieved, it be will be defined as the subject's pain maintenance dose for the remainder of the trial.

In addition to pain medications, other aspects of the background care regimen (including wound care, dialysis parameters, other concomitant medications relevant to the management of CUA; Section 4.7.3) should be stabilized (or maintained if already stable) and recorded.

Screening Visit 2

At Screening Visit 2, the CUA lesions identified at Screening Visit 1 and confirmed as CUA lesions by the central wound rating group, will be evaluated for significant improvement, based on the opinion of the Investigator, since the initial assessment. If the CUA lesion has not significantly improved, in the opinion of the investigator, any incomplete eligibility criteria should be

completed, including Holter monitoring and local ECGs. Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to receive either 7 mg/kg of SNF472 or matching placebo.

A subject who does not meet all of the eligibility criteria will be screen failed. Subjects who have failed screening may be rescreened on a case-by-case basis after discussion with the Medical Monitor.

Due to visit scheduling, a subject's Week 1 Day 1 visit may occur up to 7 days after randomization. If during this period and prior to the administration of the first dose of study drug the Investigator observes changes to the primary lesion (e.g., significant improvement from screening) or changes to the subject's clinical condition which may make the subject ineligible, the Medical Monitor should be consulted.

5.2 PART 1: DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TREATMENT PERIOD

The schedule of assessments during Part 1 is provided in Table 1.

Subjects will receive SNF472 or placebo for 12 weeks in addition to background care (in accordance with the clinical practices of each site). No changes to the background care regimen, including pain maintenance dose, should be made after randomization unless medically indicated in the opinion of the Investigator. Medically indicated changes to background care will be recorded on the eCRF.

In Part 1, subjects should continue to record all pain medications taken in the pain medication diary and bring their diary with them to each visit. Diaries should be reviewed with the subject at least weekly and pain medications will be recorded in the eCRF.

5.3 PART 2: OPEN-LABEL TREATMENT PERIOD

The schedule of assessments during Part 2 is provided in Table 2.

Subjects who complete Part 1 will be eligible to participate in Part 2, in which all subjects will receive open-label SNF472 for 12 weeks and continue stable background care (in accordance with the clinical practices of each site), including pain maintenance dose, with no changes unless medically indicated in the opinion of the Investigator. Medically indicated changes to background care will be recorded on the eCRF.

In Part 2, subjects should continue to record all pain medications taken in the pain medication diary and bring their diary with them to each visit. Diaries should be reviewed with the subject at least weekly and pain medications will be recorded in the eCRF.

If a visit is missed in Part 1 or Part 2, subjects should return to the normal schedule after the missed visit. Missed assessments should be conducted at the next visit.

5.4 FOLLOW-UP PERIOD/ EARLY TERMINATION

The schedule of assessments for the Follow-Up/ Early Termination is provided in Table 2.

Subjects completing the study will return for a follow-up visit 4 weeks after the last dose of study drug. Subjects should continue on stable background care during the 4-week follow-up period with no changes unless medically indicated in the opinion of the Investigator. Subjects who discontinue study drug during Part 1 or Part 2 will be asked to complete study assessments throughout the respective part of the study (Part 1 or Part 2) and complete a follow-up visit. Subjects who discontinue study drug and are unwilling to complete the remaining study assessments should be encouraged to return for an early termination visit 4 weeks after the last dose of study drug. Additional information on early discontinuation of study drug and withdrawal from the study is provided in Section 7.

In the follow-up period, subjects should continue to record all pain medications taken in the pain medication diary and bring their diary with them to each visit. Diaries should be reviewed with the subject at least weekly and pain medications will be recorded in the eCRF.

5.5 ORDER OF ASSESSMENTS

5.5.1 Prior to Start of Dialysis

The following should be performed prior to the start of dialysis and the following order is recommended:

1. Pain VAS
2. Wound QoL questionnaire
3. BWAT and image (photos and video) collection
4. Placement of the Holter monitor and initiation of recording with Holter monitor prior to dialysis

5.5.2 During Dialysis

When more than one of the following assessments is conducted at the same time point, they should be performed in the following order:

1. Perform local ECGs (see Section 5.8.5 for time points)
2. Blood sampling for ionized calcium and safety labs
3. Blood sampling for biomarkers, PD, and PK

Data will be recorded in an eCRF implemented in an appropriate EDC system, as described in Section 9.2.

5.6 EFFICACY ASSESSMENTS

5.6.1 Wound Evaluation

Using a standardized device and imaging software, images (photos and videos) of CUA lesions will be acquired and stored, according to details provided in the Site Imaging and BWAT Manual at the visits specified in Table 1 and Table 2. The course of the lesion(s) will be assessed

quantitatively with BWAT (Section 5.6.1.1) and with qualitative image review (Section 5.6.1.2). If a subject has more than one CUA lesion, the course of up to 3 lesions (primary, secondary, tertiary) will be assessed. Which lesions are primary, secondary, and tertiary will be defined based on the total area as measured by the wound imaging software at screening. In addition, occurrence of new CUA lesions will be monitored (Section 5.6.1.3).

The central wound rating group will review image quality and notify the site if wound imaging needs to be repeated at a following visit for a technical reason.

5.6.1.1 Quantitative Wound Evaluation with BWAT and BWAT-CUA

The BWAT (APPENDIX 1; Bates-Jensen and Sussman, 2011) is a standardized tool for quantitative assessment of wound healing that includes evaluation of these 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
- Epithelialization

Each item is rated on a scale of 0 or 1 (best) to 5 (worst). Two scores will be calculated as endpoints for this study, BWAT total and BWAT-CUA. BWAT total is the sum of all 13 items with a possible range of scores from 9 to 65. In addition, a targeted modification of BWAT, the BWAT-CUA, will be calculated which focuses on the following prototypical features of CUA lesions: necrotic tissue type, necrotic tissue amount, exudate type, exudate amount, skin color surrounding wound, peripheral tissue edema, peripheral tissue induration, and granulation tissue. The possible range of scores for BWAT-CUA is 8 to 40.

Two additional items are collected in BWAT, location and shape, but do not contribute to the scoring.

Site personnel will be trained and responsible for obtaining quality wound photographs and videos with the provided device and imaging software, along with scoring undermining, peripheral tissue edema, and peripheral tissue induration, according to the procedures

described in the Site Imaging and BWAT Manual. Every effort should be made for the same person at the site to perform evaluation of these items at all visits for each subject. As with all other study personnel, the central wound rating group will be blinded to treatment assignment. The central raters will review the site's ratings and will rate the remaining BWAT items based upon review of the photographs and videos. Rating of the size item will be aided by automated measurements from the imaging software. The scoring procedure will be described in detail in the Central Wound Rating Charter.

5.6.1.2 Qualitative Wound Evaluation

The central wound rating group will perform a qualitative review of the baseline (Week 1 Day 1) and Week 12 images of the primary lesion after the completion of the Week 12 visit. The Week 12 wound will be assigned to one of the following categories:

- Worsened from baseline
- Equal to baseline
- Improved from baseline

A similar qualitative comparison will be made between Week 12 and Week 24 images of the primary lesion after the completion of the Week 24 visit.

Qualitative reviewers will not be involved in confirmation of CUA lesions or BWAT rating during the trial. In addition to being blinded to treatment assignment in Part 1, the qualitative reviewers will be blinded to the order of study visits in both Part 1 and 2. The review procedure is described in detail in the Central Wound Rating Charter.

5.6.1.3 New CUA Lesions

Occurrence of new CUA lesions since baseline (Week 1 Day 1) will be monitored periodically as specified in Table 1 and Table 2 to assess overall lesion burden. The site will collect images of the suspected CUA lesion(s) that were not present at baseline and the central wound rating group will review the images (according to the procedure described in Central Wound Rating Charter) to determine whether the new lesion is a CUA lesion. BWAT-CUA and BWAT total will not be scored for the new CUA lesions.

5.6.2 Pain VAS

The Pain VAS will be used to assess the level of CUA wound-related pain experienced by the subject in reference to all of the subject's lesions. A VAS is an instrument that aims to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured.

Pain VAS will be electronically administered, requiring the subject to mark a position anywhere on a 10-cm (100-mm) long horizontal line to indicate the worst wound-related pain experienced during the previous 24 hours. From this mark, the VAS score will be electronically recorded in mm based on measurement along the line. The VAS line will be anchored by the word

descriptors at each end of “no pain” and “worst possible pain”. An example of a Pain VAS is illustrated in Figure 3.

Figure 3. Pain Visual Analog Scale

5.6.3 Wound-QoL

The Wound-QoL questionnaire, provided in APPENDIX 2, measures the disease-specific, health-related QoL of patients with chronic wounds. It consists of 17 items on impairments that are assessed in reference to the preceding 7 days. Each rated on a 5-point Likert scale with responses ranging from “not at all” (0) to “very much” (4).

The Wound-QoL will be electronically administered. The global score and subscale scores will be calculated programmatically in accordance with the scoring rules.

5.6.4 Pain Medications

Subjects will record all pain medications used in a daily pain medication diary. Site staff will review the diary with subjects at least weekly and record actual pain medications used in the eCRFs.

5.7 PHARMACODYNAMICS, PHARMACOKINETICS, AND BIOMARKER ASSESSMENTS

Blood samples for PD, PK, and biomarker analyses must be collected on a dialysis day when study drug dosing occurs. Samples will be obtained from the dialysis port and should be either stored in a -80°C (±10°C) freezer prior to shipment or be shipped on dry ice on the same day as collection. Samples for PK, PD, and biomarker analyses will be collected pre-dose and within 20 minutes prior to the end of infusion (EOI)at Weeks 1, 12, 13, and 24. For the follow-up/early termination visit, the biomarker sample should be collected prior to the start of dialysis.

Collection (including sample volumes), storage, and handling of blood samples for PD, PK, and biomarker analyses will be detailed in the Laboratory Manual.

The PD, PK, and biomarker analyses summarized in Sections 5.7.1, 5.7.2, and 5.7.3, respectively, will be performed at central laboratories.

5.7.1 Pharmacodynamics

The PD of SNF472 will be assessed in pre-dose and EOI samples by an in vitro method to determine the propensity for HAP crystal formation in plasma.

5.7.2 Pharmacokinetics

The plasma concentration of SNF472 will be determined in pre-dose and EOI samples. The EOI sample corresponds to C_{max}.

5.7.3 Biomarkers

The following biomarkers will be assessed in pre-dose and EOI samples: fetuin A, intact fibroblast growth factor 23 (iFGF23), c-terminal fibroblast growth factor 23 (c-FGF23), matrix gla protein (MGP), sclerostin, growth differentiation factor 15 (GDF15), tartrate-resistant acid phosphatase 5b (TRAP5b), bone alkaline phosphatase (BALP), Dickkopf WNT signaling pathway inhibitor 1 (DKK1), osteocalcin, osteoprogeterin, osteopontin, bone morphogenetic protein-9 (BMP-9), iron, ferritin, and transferrin, and lipids (LDL, HDL, total cholesterol, triglycerides). Biomarker testing may include RNA measurements. No DNA testing will be performed.

5.8 SAFETY ASSESSMENTS

The safety assessments described in this section will be performed at the visits specified in Table 1 and Table 2.

5.8.1 Adverse Events

The assessment and reporting of AEs are discussed in detail in Section 6.

5.8.2 Medical History

The subject's relevant medical history will be recorded at screening. Previous illnesses and history of drug and alcohol abuse will be recorded. Medical history will be updated prior to the first day of dosing in Part 1.

5.8.3 Physical Examination and Body Weight

The physical examination will include an examination of general appearance, skin, head and neck, chest, lungs, heart, abdomen, extremities and basic nervous system evaluation. If any physical findings are abnormal, the Investigator must document the abnormality as nonclinically significant (NCS) or clinically significant (CS). Subsequent to the screening examination, any abnormality assessed as 'CS' must be recorded as an AE if not explained by a coexisting condition (documented in the medical history).

Physical examinations will include body weight which will be recorded post-dialysis, without shoes. If body weight cannot be assessed without shoes, then it should be assessed under the same conditions throughout the study. Height will be included in the physical examination at screening only.

5.8.4 Vital Signs

Vital signs (heart rate, systolic and diastolic blood pressures, respiratory rate, and body temperature) will be assessed post-dialysis after the subject has been sitting for 5 minutes. The results of these protocol-specified assessments will be recorded in the eCRF; however, additional vital signs assessments taken as part of background care do not need to be recorded.

5.8.5 Holter Monitoring and Electrocardiograms

Holter monitoring and local ECGs must be completed on dialysis days and, with the exception of screening visits, only on a day when the study drug is administered. Holter monitoring during dialysis will be performed as part of Screening Visit 2 (may be conducted at any dialysis session during the last week of screening prior to Week 1 Day 1), and at Weeks 1, 6, 12, 13, and 24. The Holter monitor will be placed on the subject and the recording started prior to the beginning of dialysis (at least 30 minutes) and continue to the end of dialysis.

Holter instruction and timing are summarized in Table 4. Refer to the Holter and ECG Manual for additional details and procedures.

Table 4. Holter Instructions and Timing

Visit	Holter Instructions and Time Point Collection
Screening Visit 2	Start Holter recording prior to the start of dialysis (at least 30 minutes). Record the start time of dialysis. Record the stop time of dialysis and manually end the Holter recording.
Week 1 Day 1	Start Holter recording prior to the start of dialysis (at least 30 minutes). Record the start time of dialysis. Collect times of start and end of study drug infusion. Record the stop time of dialysis and manually end the Holter recording.
Week 6 Day 3 (± 2 days)	
Week 12 Day 5	
Week 13 Day 1	
Week 24 Day 5	

Local ECGs will be obtained using the ECG instrument that will be supplied with the Holter monitor and will be assessed for abnormalities by the Investigator. The Screening Visit 2 ECGs should be recorded at the start of dialysis and 2.5 hours after the start of dialysis and may be conducted at any dialysis session during the last week of screening prior to Week 1 Day 1. Local ECGs should be obtained pre-dose and within 20 minutes prior to EOI at Weeks 1, 12, 13, and 24. Abnormalities the Investigator judges to be clinically significant should be recorded as adverse events. These ECGs should be considered source documentation and be included as part of the subject's chart.

Local ECG collection timepoints are summarized in Table 5. For additional details on local ECG procedures refer to the Holter and ECG Manual.

Table 5. Local ECG Tracing Collection Timepoints

Visit	ECG Tracing Collection Timepoints
Screening Visit 2	Start of Dialysis
Screening Visit 2	2.5 hours after the start of dialysis
Week 1 Day 1	Pre-dose
Week 1 Day 1	Within 20 minutes before the End of Infusion
Week 12 Day 5	Pre-dose
Week 12 Day 5	Within 20 minutes before the End of Infusion
Week 13 Day 1	Pre-dose
Week 13 Day 1	Within 20 minutes before the End of Infusion
Week 24 Day 5	Pre-dose
Week 24 Day 5	Within 20 minutes before the End of Infusion

5.8.6 Laboratory Evaluations

Laboratory parameters to be evaluated during this study are provided in Table 6. Blood samples will be collected via the dialysis port pre-dose for these laboratory evaluations. Blood samples for the assessment of ionized calcium will also be collected at EOI at specified visits (within 20 minutes prior to the end of the study drug infusion) and must be shipped on day of collection under ambient conditions to the central laboratory.

Collection (including sample volumes), storage, and handling of the blood samples will be detailed in the Laboratory Manual. Safety laboratory sample analyses will be performed at the central laboratory in accordance with standard laboratory procedures, as specified in the Laboratory Manual.

Table 6. Laboratory Parameters

Hematology	Hematocrit Hemoglobin (including MCV, MCH, MCHC) Platelet count White blood cell (WBC) count (total and differential)	
Chemistry	Alanine transaminase (ALT) Albumin Alkaline phosphatase (ALP) Aspartate transaminase (AST) Bicarbonate Blood urea nitrogen (BUN) Calcium, total Calcium, ionized Chloride Creatine kinase (CK) Creatinine Gamma-glutamyl transpeptidase (GGT) Glucose (non-fasting)	hs-CRP Lactic acid dehydrogenase (LDH) Magnesium Parathyroid hormone (PTH, intact) Phosphate/phosphorus Potassium Sodium Total bilirubin Total protein Uric acid Vitamin K
Other	Serum pregnancy test (females of childbearing potential only)	

6 ADVERSE EVENTS

6.1 DEFINITIONS

6.1.1 Adverse Event

An AE is defined by the ICH Guideline for Good Clinical Practice (ICH GCP) as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.

A treatment-emergent AE is defined as an AE that begins or that worsens in severity after at least one dose of the study drug has been administered.

Surgical procedures or laboratory values themselves are not AEs. Surgical procedures are therapeutic measures for conditions that require surgery. Abnormal laboratory values may lead to diagnosis of a condition. The condition for which the surgery or laboratory value is indicative of is an AE if it occurs or is detected during the study period. Planned surgical measures and the condition(s) leading to these measures are not AEs if the condition(s) was (were) known before the period of observation. In the latter case the condition should be reported as medical history.

6.1.2 Serious Adverse Event

An SAE is an AE that at any dose (including overdose) that meets at least one of the following criteria:

- Results in death
- Is life-threatening (i.e., the subject was at immediate risk of death at the time of the SAE; it does not refer to a SAE that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization (i.e., a hospital inpatient admission or prolongation of hospital stay was required for the treatment of the AE, or that one or the other occurred as a consequence of the event)
- Results in persistent or significant disability or incapacity (i.e., a permanent or significant and substantial disruption of a person's ability to carry out normal life functions)
- Is a congenital anomaly or birth defect
- Is an important medical event (If an AE doesn't meet one of the criteria above, but the Investigator considers the event to be clinically important, then the event could be classified as an SAE under the criterion of 'important medical event'. Examples of such medical events may include bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that don't result in inpatient hospitalization.)

6.1.3 Wound-Related Complications

Each adverse event will be assessed as CUA wound-related or not CUA wound-related by the Investigator or designee.

6.1.4 Adverse Event by Severity or Intensity

Assessment of severity of an AE will be rated by the Investigator or designee according to the criteria in Table 7.

Table 7. Definitions of Adverse Events Severity Based on CTCAE

Grade 1 (Mild)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 (Moderate)	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental ADL[1].
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2]
Grade 4 (Life-Threatening)	Life-threatening consequences; urgent intervention indicated.
Grade 5 (Fatal)	Death related to AE

ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events.

[1] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[2] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

It is important to note that severity and seriousness are separate characteristics of an AE: severity denotes the intensity of the AE (Table 7), whereas seriousness is an AE categorization based on the criteria listed in Section 6.1.2 that denotes whether expedited reporting is required for an AE (see Section 6.3.1.2 and Section 6.3.2).

Any AE with a severity of Grade 4 or 5 would meet the criteria for seriousness. A Grade 3 AE may or may not meet the criteria for seriousness depending upon whether any of the other criteria for seriousness in Section 6.1.2 are met.

6.1.5 Relationship between Adverse Events and Study Drug

The relationship between all AEs and the study drug must be assessed the Investigator or clinician designee based on the temporal relationship and his/her clinical judgement using the guidelines in Table 8. In addition to a temporal relationship, the Investigator should consider the following when determining the relationship between an AE and study drug: whether an alternative etiology has been identified, mechanism of action of the study drug, and/or the biological plausibility of a relationship.

Table 8. Guidelines for Assessing the Potential Relationship Between Adverse Event and the Study Drug

Related	This causal relationship is assigned if the AE is known to occur with the study drug, there is a reasonable possibility that the study drug caused the AE, or there is a temporal relationship between study drug administration and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study drug and the AE.
Not Related	This causal relationship is assigned when there is not a reasonable possibility that the administration of the study drug caused the event, there is no temporal relationship between the study drug administration and event onset, or an alternate etiology has been established.

6.1.6 Adverse Event Outcome

If the same AE occurs more than one time in the same subject, then the AE in question must be documented and assessed as a new event each time, unless the AE is considered to be a continuation of the previously reported event rather than a reoccurrence of the event.

The AE outcome will be recorded as defined in Table 9.

Table 9. Adverse Event Outcome

Not recovered/not resolved - One of the possible results of an AE outcome that indicates that the event has not improved or recuperated.
Recovered/resolved - One of the possible results of an AE outcome that indicates that the event has improved or recuperated. The subject recovered from the AE.
Recovering/resolving - One of the possible results of an AE outcome that indicates that the event is improving.
Recovered/resolved with sequelae - One of the possible results of an AE outcome where the subject recuperated but retained pathological conditions resulting from the prior disease or injury.
Unknown - There is an inability to access the subject or the subject's records to determine the outcome (i.e., subject withdraws consent or is lost to follow-up).
Fatal - The AE directly caused death.

6.1.7 Abnormal Laboratory Values

The Investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in a subject represents a clinically significant change from subject's baseline value (Week 1, Day 1). In general, abnormal laboratory findings without clinical significance

(based on the Investigator's judgment) or not requiring treatment should not be recorded as AEs.

6.1.8 Pregnancy and In Utero Drug Exposure

Since SNF472 has not been evaluated in pregnant or nursing women, the treatment of pregnant women or women of childbearing potential who are not using effective contraception is contraindicated (see Section 4.7.4.2 for instructions on birth control).

Pregnancies occurring in female subjects, or female partners of male subjects are considered immediately reportable events if the pregnancy occurs during the study treatment through 30 days after the subject's last dose of study drug. If a pregnancy occurs in a subject, study drug must be discontinued immediately.

The pregnancy must be reported to the Sponsor or designee within 24 hours of the Investigator's knowledge of the pregnancy using the Pregnancy Notification Form.

The Investigator will follow the pregnant subject until completion of the pregnancy and must notify the Sponsor of the pregnancy outcome within 24 hours of the Investigator's knowledge of the outcome. The Investigator will provide this information on the Pregnancy Outcome Report Form. This notification includes pregnancies resulting in live, "normal" births.

If the pregnant subject experiences an SAE during pregnancy, or the outcome of the pregnancy meets any of the serious criteria (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs specified in Section 6.3.1.2.

All neonatal deaths and congenital anomalies that occur within 30 days of birth (regardless of causality) should be reported as SAEs to the Sponsor or designee. In addition, any infant death or congenital anomaly occurring after 30 days that the Investigator suspects is related to the in utero exposure to the study drug should also be reported to the Sponsor or designee.

6.2 HEMODIALYSIS-RELATED EVENTS

The following events are known to occur during HD treatments and should be recorded in the eCRF as HD-related events rather than AEs. However, they should be recorded as AEs if they are considered to be unrelated to the HD treatment procedure or if they worsen in severity or increase in frequency during HD compared to baseline (Week 1 Day 1).

- Hypotension
- Muscle cramps
- Disequilibrium syndrome
- Nausea
- Vomiting
- Headache
- Fatigue

- Chest pain
- Itching
- Fever
- Chills
- Pyrogen reaction
- Hypertension

6.3 DOCUMENTATION AND REPORTING OF ADVERSE EVENTS

6.3.1 Documentation and Reporting of Adverse Events by Investigator

6.3.1.1 Recording of Adverse Events

AEs will be collected from the first time a subject receives study drug until completion of either the follow-up visit or an early termination visit. For subjects who discontinue study drug early and agree to complete all study assessments, all AEs should be collected until the follow-up visit. Subjects who discontinue study drug early and withdraw consent for completing further study assessments should complete an early termination visit 4 weeks after last dose of study drug and all AEs should be collected up to that time.

All AEs after informed consent signature but before the first dose of study drug should be captured as medical history.

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the event has resolved or stabilized, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until study follow-up is complete.

All AEs, regardless of the relationship to study drug, will be recorded. All AE reports should contain a brief description of the event, date, and time of onset, date and time of resolution, severity, seriousness, treatment required, causal relationship to study drug, action taken with the study drug, and outcome.

In general, an AE that is the primary cause of subsequent events should be identified by the primary cause (e.g., for dehydration due to diarrhea, the AE would be diarrhea). However, AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events (e.g., sepsis secondary to pneumonia, both events should be recorded).

6.3.1.2 Reporting of Serious Adverse Events

All SAEs that occur during the period of observation (see Section 6.3.1.1) whether considered to be associated with the study drug or not, must be entered in the eCRF for reporting within 24 hours of the Investigator's first knowledge of the event. An alternative method of reporting will be provided to sites if eCRF access is not available.

The Investigator should not delay initial SAE report entry due to missing data. As soon as the minimum information is available, and no later than 24 hours after becoming aware of the SAE, the initial SAE report will be entered into eCRF.

If necessary, the Investigator will provide follow-up reports in a timely manner after knowledge of further relevant information.

Detailed SAE reporting instructions and training will be provided to study site personnel.

6.3.2 Reporting of Adverse Events to Regulatory Authorities and Independent Ethics Committees/Institutional Review Boards

The Sponsor or designee will be responsible for informing the regulatory authority of SAEs according to local requirements.

The Sponsor or their designee will provide annual safety reports to the regulatory authorities, as applicable. These updates will include information on suspected unexpected serious adverse reactions (SUSARs) and other relevant safety findings.

The Sponsor or designee will notify regulatory authorities of any AE that is serious, unexpected, and related to study drug (i.e., a SUSAR) according to applicable local safety reporting requirements.

The Sponsor or designee will notify the Investigators of SUSARs that are submitted to regulatory authorities according to local country requirements.

The Investigator will be responsible for informing the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of SAEs and SUSARs according to local requirements.

6.4 DATA AND SAFETY MONITORING BOARD

To minimize the possibility of exposing subjects to unusual risk, an external independent DSMB has been established. The DSMB will review safety data on a regular basis and will make recommendations to the Sponsor as to whether or not to continue the study. The roles and responsibilities of the DSMB are defined in the DSMB Charter.

7 DISCONTINUATION AND WITHDRAWALS

7.1 DISCONTINUATION OF STUDY DRUG

Subjects may discontinue study drug at any time. The reasons for which a subject may discontinue from study drug include, but are not limited to, the following:

- AE
- Subject request
- Protocol violation

- Investigator's determination that discontinuation from treatment is appropriate (with documentation of the reason)
- Discontinuation of study drug due to a CTCAE Grade 4 AE that is considered by the Investigator to be related to the study drug and not due to comorbidities or the disease.

Subjects may request to stop study drug at any time without penalty and for any reason without prejudice to his/her future medical care.

If a subject requests to discontinue study drug, the Investigator should discuss the subject's reasons for this request with the subject, including asking about the possible contribution of adverse events to the request. Based upon the subject's responses, the Investigator should encourage the subject to continue receiving study drug if the subject's concerns can be addressed. If the subject still requests to discontinue study drug, the reason for the request will be recorded in the eCRFs.

Subjects who discontinue study drug during Part 1 should be asked to continue to complete all study assessments through the end of Part 1 and the follow-up visit as if they had remained on study drug. These subjects are not eligible to participate in Part 2 of the study.

Subjects completing Part 1 who subsequently discontinue SNF472 during Part 2 should be asked to continue to complete all study assessments through the end of Part 2 and the follow-up visit as if they had remained on SNF472.

Adverse events will continue to be collected from subjects who request early discontinuation from the study drug during Part 1 or Part 2 but continue to participate in the trial assessments for remaining visits.

All subjects requesting early discontinuation and withdrawal of consent for follow-up visits should be informed of the potential greater public health value of the study if they complete the follow-up assessments and visits.

7.2 WITHDRAWAL OF SUBJECT FROM THE STUDY

Subjects may be withdrawn from the study for any of the following reasons including but not limited to:

- Pregnancy
- AE (including CTCAE Grade 4 AE considered related by Investigator as defined above)
- Subject request/ withdrawal of consent
- Investigator's determination that discontinuation from treatment is appropriate (with documentation of the reason)
- Death
- Discontinuation of the study or the study center by Sponsor's decision

Subjects who discontinue study drug and are unwilling to complete the remaining study assessments will be encouraged to return for an early termination visit 4 weeks after the last

dose of study drug to complete the procedures outlined in the Schedule of Assessments (Table 2). Subjects who withdraw consent for continuing assessments and follow-up visits and for non-patient contact (e.g., medical records check) will be asked to sign the withdrawal of consent form, indicating withdrawal of consent for the remaining follow-up visits, assessments, and/or disallowing further access to their medical records.

If a subject is withdrawn from the study due to an AE, the subject should continue to be provided medical care. This may include, if needed, referral to another physician. The AE that led to study withdrawal should be followed until an outcome can be defined.

If a subject withdraws consent from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such refusal for further follow-up.

7.3 STORAGE OF SAMPLES

Blood samples collected for PK, PD, and biomarker analyses will be stored under the control of the Sponsor for a maximum of 1.5 years after study end and then destroyed.

8 STATISTICAL METHODS

The methods for the planned statistical analyses of efficacy, PK, PD, and safety endpoints are summarized in the following sections. Statistical analyses for additional parameters (e.g., subject characteristics, disposition, exposure, compliance); and more detailed descriptions of the methods presented in this section will be provided in the statistical analysis plan (SAP). Any major deviations from the planned analyses specified in the protocol and SAP will be documented in the clinical study report.

8.1 ENDPOINTS

Unless otherwise indicated “baseline” refers to the assessment on Week 1, Day 1.

8.1.1 Efficacy Endpoints

In Part 1, the primary, secondary, and exploratory efficacy endpoints will compare the placebo and SNF472 groups as follows:

Alternate Primary Efficacy Endpoints:

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

Secondary Efficacy Endpoints (assessed hierarchically):

- Absolute change from baseline to Week 12 in the Wound-QoL score

- Absolute 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
- Rate of change in opioid use as measured in morphine milligram equivalents (MME) from baseline to Week 12

Exploratory Efficacy Endpoints:

- Absolute change from baseline to Week 12 in wound size for the primary lesion
- Absolute change from baseline to Week 12 in each BWAT item for the primary lesion
- Absolute change in BWAT-CUA, BWAT total, Pain VAS, and Wound-QoL score by visit
- Proportion of subjects with new CUA lesions between baseline and Week 12
- Absolute change from baseline to Week 12 in the Wound-QoL scores for the body, everyday life, and psyche subscales
- Absolute change from baseline to Week 12 in the BWAT-CUA score for the secondary and tertiary lesions
- Proportion of subjects requiring an increase in pain medication related to their CUA lesion(s) between baseline and Week 12
- Proportion of subjects with a decrease in pain medication related to their CUA lesion(s) between baseline and Week 12
- Absolute change from baseline to Week 12 in opioid use as measured in MME

In Part 2, the exploratory efficacy endpoints will be within-group comparisons for the following:

- Absolute change from baseline to Week 24 vs Week 12 in the BWAT-CUA score for the primary lesion
- Absolute change from baseline to Week 24 vs Week 12 in the Pain VAS score
- Absolute change from baseline to Week 24 vs Week 12 in the Wound-QoL score
- Absolute change from baseline to Week 24 vs Week 12 in the BWAT total score for the primary lesion
- Qualitative wound image evaluation for the primary lesion at Week 24 vs Week 12 (worsened, equal to, or improved relative to baseline)
- Absolute change from baseline to Week 24 vs Week 12 in wound size for the primary lesion
- Absolute change from baseline to Week 24 vs Week 12 in each BWAT item for the primary lesion

- Absolute change from Week 24 to the follow-up visit in the BWAT-CUA score for primary lesion
- Absolute change from Week 24 to the follow-up visit in the Pain VAS score

8.1.2 Pharmacodynamic and Biomarker Endpoints

- Percent inhibition of HAP crystallization between pre-dose and EOI at Weeks 1, 12, 13, and 24
- Changes in biomarker concentrations from baseline to Week 12 and from Week 13 to Week 24
- Changes in biomarker concentrations between pre-dose and EOI at Weeks 1, 12, 13, and 24

8.1.3 Pharmacokinetic Endpoints

- Concentration of SNF472 in pre-dose and EOI at Weeks 1, 12, 13, and 24

8.1.4 Safety Endpoints

- Proportion of subjects with AEs, SAEs, and deaths
- Changes from baseline in the following:
    - Laboratory parameters
    - Holter monitoring results
    - QTc interval and other ECG parameters
    - Vital signs
- Proportion of subjects with a CUA wound-related infection, sepsis, hospitalization, or any CUA wound-related complication

8.2 DETERMINATION OF SAMPLE SIZE

8.2.1 Planned Sample Size

The sample size calculation is based on the effect sizes and standard deviations (SD) observed for changes in BWAT-CUA and Pain VAS from baseline to Week 12 in the Phase 2 study (SNFCT2015-04). The effect sizes for BWAT-CUA and Pain VAS were 6.3 and 24 units, respectively, with SDs of 6.5 and 31.4 units. Assuming similar results and based on 1,000,000 trial simulations, a sample size of 66 subjects (33 per group) will provide an overall power of between 95.1% and 99.0% (corresponding to correlations between test statistics of ρ = 0.90 to 0) when the alternate primary endpoints are tested using a Hochberg closed test procedure with a 4% alpha level, 2-sided.

8.2.2 Sample Size Re-Estimation

A SSRE procedure is planned when primary endpoint data is available from approximately 33 of the planned total of 66 subjects randomized and treated for 12 weeks. This procedure will be conducted blind to the Sponsor by a fully independent statistical service provider. The conditional power (CP) will be computed for both alternate primary endpoints, BWAT CUA and Pain VAS, using the methods described by Mehta and Pocock (2011). Table 10 gives the decision rule with regards to continuation of the study with or without a sample size increase. Any increase in sample size will be capped at 50% of the planned sample size (i.e., the maximum total sample size will be capped at 66 + 1/2 x 66 = 99 subjects). With 100,000 trial simulations, this procedure was shown not to inflate the overall type I error and, hence, no alpha adjustment is required in the final analysis.

Table 10. Decision Rules for Sample Size Increase

Conditional power		BWAT CUA			
		<10%	≥10%-<30%	≥30%-<90%	≥90%
VAS	<10%	Continue, no SS increase	Continue, no SS increase	Continue, SS increase	Continue, no SS increase
	≥10%-<30%	Continue, no SS increase	Continue, no SS increase	Continue, SS increase	Continue, no SS increase
	≥30%-<90%	Continue, SS increase	Continue, SS increase	Continue, SS increase	Continue, no SS increase
	≥90%	Continue, no SS increase	Continue, no SS increase	Continue, SS increase	Continue, no SS increase

The CP computed as per Mehta and Pocock (2011) will give rise to two CP values, CP_1 and CP_2, for each of the two primary endpoints respectively; based on these CP values, Equation 9 in Mehta and Pocock (2011) will be used to compute the corresponding post-interim sample sizes, $\tilde{n}_1$ and $\tilde{n}_2$, required to deliver the cross tabulated power as displayed in Table 10. This, in turn, will give two new sample size totals for the study, N_1 and N_2, relating to the two primary endpoints. The larger of N_1 and N_2 will be taken as the revised sample size for the study subject to a maximal increase of 99 subjects (i.e., at most a 50% increase over the planned sample size of N=66 subjects). The final analysis will then combine the pre- and post-interim z-values for each of the two primary endpoints using NOT the approach suggested by Mehta and Pocock 2011 but rather the approach defined by Cui et al (1999) which guarantees no alpha inflation regardless of how the post-interim sample sizes (i.e., $\tilde{n}_1$ and $\tilde{n}_2$) are determined.

The independent statistical service provider will provide the conditional power and sample size computations to the independent DSMB only. The DSMB will review these results and the

associated decision rule from Table 10 and provide only the sample size recommendation to the Sponsor. The Sponsor will not receive the conditional power assessments.

Finally, the Sponsor retains full discretion with regards to the outcome of the sample size re-estimation procedure and may decide to continue the trial with the sample size increased as described above or unchanged.

8.3 ANALYSIS POPULATIONS

The following analysis populations will be defined: Safety, modified Intent-to-Treat (mITT), Per Protocol (PP), PK, and PD.

The Safety population will consist of all randomized subjects who receive at least one dose of study drug. Subjects will be analyzed according to the treatment they received. The Safety analysis population will be used for analyses of safety endpoints.

The mITT population will consist of all enrolled subjects who are randomized, receive at least one dose of study drug, and have at least one post-randomization efficacy evaluation. Subjects will be analyzed according to the treatment to which they were randomized. Consistent with ICH E9, the mITT population will be the primary analysis population for efficacy endpoints.

The PP population will be the subset of subjects in the mITT population who do not have major protocol violations, have evaluable primary efficacy data, and have received a pre-specified minimum study drug exposure. The PP population will be used for supportive analyses of efficacy endpoints. Additional details will be outlined in the Statistical Analysis Plan.

The PK population will consist of all subjects who are randomized and receive at least one dose of study drug and for whom the primary PK parameter (C_{max}) can be calculated.

The PD population will consist of all subjects who are randomized and receive at least one dose of study drug and for whom both pre-dose and EOI HAP crystallization inhibition can be calculated for at least one timepoint.

8.4 SUBGROUPS, COVARIATES, AND STRATA

The primary and secondary efficacy endpoint analyses will be stratified by STS use at randomization. For endpoints measuring change from baseline, baseline values of the efficacy variable will be included in statistical models as covariates. The following subgroups may be explored for the primary and secondary endpoints: age, sex, race, region, and major comorbid conditions (e.g., diabetes mellitus, peripheral vascular disease).

8.5 GENERAL STATISTICAL CONSIDERATIONS

Efficacy, PK, PD, biomarker, and safety data will be summarized descriptively using mean, median, SD, standard error (SE), first quartile (Q1), third quartile (Q3), minimum, and maximum values for continuous variables and using counts (n) and percentages for categorical variables.

Unless specified otherwise, all baseline assessments will be based upon the Week 1, Day 1 pre-dose assessment.

8.6 EFFICACY ANALYSES

The mITT population will be the primary analysis population for all primary, secondary and exploratory efficacy endpoint analyses. Unless otherwise indicated "baseline" refers to the assessment on Week 1, Day 1.

8.6.1 Primary Efficacy Endpoint Analysis

The comparison of absolute change from baseline to Week 12 in BWAT-CUA score between treatment groups will be achieved using a mixed model repeated measures (MMRM) analysis to estimate the difference between randomized treatment group least squares means (LS means) at 12 weeks. The model will include fixed effect terms for randomized treatment, visit, and visit by randomized treatment interaction; the model will also be stratified for STS use at randomization and baseline BWAT-CUA score and will be included as covariates. Subject will be fitted as a random effect and an unstructured variance-covariance matrix will be used.

The comparison of absolute change from baseline to Week 12 in the Pain VAS score will be analyzed using an MMRM analysis similar to that for the change in BWAT-CUA score with covariates for baseline Pain VAS score and stratified for STS use at randomization.

The MMRM analysis assumes any missing data are missing at random; therefore, sensitivity analyses under the assumption of missing not at random will be used to assess the robustness of the primary MMRM analysis. These sensitivity analyses will include (i) jump to reference multiple imputation (MI) which assumes that subjects with monotone missingness in the experimental treatment arm follow the same distribution as observations from subjects in the control arm and (ii) a tipping point analysis to identify whether the penalty, if applied to subjects with missing data in the experimental treatment arm, would result in the loss of statistical significance of the primary analysis (Ouyang et al, 2017).

8.6.2 Secondary Efficacy Endpoint Analyses

The secondary endpoints will be evaluated hierarchically in the following order:

1. Absolute change from baseline to Week 12 in the Wound-QoL score
2. Absolute change from baseline to Week 12 wound healing assessed by the BWAT total score
3. Qualitative wound image evaluation for the primary lesion (worsened, equal to, or improved relative to baseline) at Week 12
4. Rate of change in opioid use as measured in MME from baseline to Week 12

The first secondary efficacy endpoint of the absolute change from baseline to Week 12 in Wound-QoL score will be analyzed using an MMRM analysis similar to that for the alternate primary efficacy endpoints with covariates for baseline Wound-QoL score and stratified for STS use at randomization.

The second secondary efficacy endpoint of the absolute change from baseline to Week 12 wound healing assessed by the BWAT total score will be analyzed with MMRM in the same fashion with baseline BWAT total score as a covariate and stratified by STS use at randomization.

The third secondary efficacy endpoint will be analyzed using generalized estimating equations with the primary result displayed in terms of the Week 12 odds ratio for SNF472 vs placebo along with the associated 95% CI and 2-sided p-value.

For the fourth secondary endpoint, the daily average opioid dose in MME will be calculated for all subjects prior to randomization and post-randomization on a weekly basis. The maintenance opioid dose will be defined as the average daily opioid dose in MME during the week prior to Screening Visit 2. To assess the extent to which opioid use may have differed between randomized treatment arms over time, the change from baseline in daily average MME value will be analyzed via a mixed model random coefficients analysis. MME data collected between Week 1 and Week 12 will be the dependent variable with random subject effects for intercepts and slopes. Fixed effects for randomized treatment, baseline MME value, week, and randomized treatment-by-week interaction will be included and an unstructured covariance matrix assumed to estimate the rate of change of opioid use over time for both SNF472 and placebo and assess whether the rate of use differs between randomized treatments. The treatment effect will therefore be the contrast between SNF472 and placebo slope estimates over 1 to 12 weeks. The associated slope estimates, difference in slopes, CI, and two-sided p-value will be extracted from the model and presented.

For each of the secondary endpoints, sensitivity analyses to explore the influence of missing data will be performed using multiple imputation and tipping point analyses.

8.6.3 Overall Type I Error Control

With two alternate primary endpoints assessed using a closed test procedure followed by secondary endpoints tested hierarchically (if at least one of the alternate primary endpoints is statistically positive), there is no scope for Type I error inflation if SNF472 is fully in the null, i.e., is identical to placebo treatment. However, if it is assumed that SNF472 is simultaneously a placebo for one alternate endpoint yet is a highly effective treatment for the second, the overall Type I error rate can be inflated when testing is extended to the secondary endpoints. To prevent any overall Type I error inflation the alternate primary endpoints will be assessed using a Hochberg procedure with a 2-sided alpha level of 4%. If both alternate primary endpoints are met, the alpha apportioned will be recycled so that the secondary endpoints will be assessed at the 5% alpha level, 2-sided. If only one of the alternate primary endpoints is met, the secondary endpoints will be assessed at the 1% alpha level, 2-sided.

8.6.4 Exploratory Efficacy Endpoint Analyses

Briefly, mean changes over time will be assessed using MMRM modelling, binary response endpoints will be assessed using generalized linear mixed effect modelling, and time-to-event endpoints will be assessed using Kaplan-Meier analysis. Given these analyses are exploratory, they will not be subject to Type I error control, nominal p-values will be presented and interpreted accordingly.

8.7 PHARMACODYNAMICS ANALYSES

At Weeks 1, 12, 13, and 24 the level of HAP crystal formation in EOI samples will be compared to the level of HAP crystal formation in the pre-dose sample and will be reported as a percent (%) inhibition of crystallization.

Percent inhibition of HAP crystallization between pre-dose and EOI at Weeks 1, 12, 13, and 24, will be analyzed using descriptive statistics.

8.8 PHARMACOKINETICS ANALYSES

The PK endpoint, SNF472 plasma concentrations pre-dose and EOI at Weeks 1, 12, 13, and 24, will be analyzed using descriptive statistics. Accumulation effects will be assessed by comparing the individual and mean EOI plasma concentrations between Weeks 1, 12, 13, and 24.

8.9 SAFETY ANALYSES

Safety endpoints will be analyzed descriptively using the Safety population. The primary analysis of safety endpoints will use the period from the first dose of study drug until 30 days after the last dose of study drug.

8.9.1 Adverse Events

All reported terms (Investigator descriptions) for AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). All treatment-emergent AEs will be summarized using counts and percentages by treatment group, study period (Part 1, Part 2, and follow-up), system organ class (SOC) classification, and preferred term. Additionally, treatment-emergent AEs in the following categories will be summarized: AEs leading to death, SAEs, AEs leading to discontinuation from the study, treatment-related AEs, AEs by Common Terminology Criteria for Adverse Events (CTCAE) severity grade, and CUA wound-related AEs. For all AE summaries, events will be counted only once for each subject by primary SOC and preferred term. When an AE occurs more than once for a subject, the maximum severity and causality will be used.

8.9.2 Hemodialysis-Related Events

HD-related events will be summarized using counts and percentages by treatment group, study period (Part 1, Part 2, and follow-up).

8.9.3 Clinical Laboratory Evaluation

Laboratory assessments and change from baseline will be summarized using descriptive statistics by panel, test, treatment group, and time point. Additionally, abnormal results will be summarized using counts and percentages by laboratory grade, panel, test, treatment group, and time point.

8.9.4 Holter Monitoring and Electrocardiograms

Holter data will be analyzed centrally by extracting triplicate ECGs from the recordings at each of the following 3 timepoints: pre-dose, EOI, and end of dialysis. The central reader will be blinded to the treatment assignment for Part 1 for the duration of the study, including Part 2 and follow-up until the study database is locked.

The results from the central reader assessment of ECGs extracted from the Holter as well as the results of the Holter will be used in the analyses. The following intervals will be summarized using counts and percentages by treatment group and time point: PR, QRS, RR, HR, uncorrected QT, QTcB, and QTcF. Details of additional analyses will be provided in the SAP.

8.9.5 Vital Signs

The change from baseline of vital signs (heart rate, systolic and diastolic blood pressures, respiratory rate, and body temperature) and body weight will be summarized with descriptive statistics by treatment group and time point.

8.9.6 CUA Wound Care

Wound care received for CUA lesions will be listed by subject.

8.9.7 Physical Examination Findings

Physical examination findings will be listed by subject.

9 DATA MANAGEMENT, MONITORING AND AUDITS

9.1 STUDY MONITORING

The Sponsor will be responsible for monitoring the study according to ICH GCP, although the actual monitoring visits may be conducted by a CRO in accordance with Sponsor requirements, as specified in the Monitoring Plan. Both central and on-site monitoring will be conducted.

Central monitoring will include data review by the monitor via the EDC off-site, with a focus on incomplete fields and fields in which potential errors could exist, based on the monitor's understanding of the data specification.

On site, the monitor will review the eCRF data entry against the source documents. Handling of queries and clarification/reconciliation of queries between the monitor and the site will be described in the Data Management Plan (DMP).

9.2 DATA CAPTURE AND VERIFICATION

Data capture and management will be conducted using multiple electronic systems (e.g., RTSM, ePRO, imaging software, and EDC). All systems will be compliant with the Health Insurance Portability and Accountability Act (HIPAA), meet all requirements for 21 Code of Federal Regulations Part 11 and Annex 11 of EUDRALEX Rules Governing Medicinal Product in the

European Union, Volume 4, Good Manufacturing Practice. The processes and responsibilities of data collection, management, and quality assurance will be specified in the DMP.

All applicable study data collected for each subject will be entered into the designated system(s) by trained study personnel according to the completion expectations. This training will be available on demand for refresher training. Study visit assessment data (e.g., vital signs, physical exam, ECG, Pain VAS, Wound-QoL, and BWAT) are expected to be entered directly into the designated system(s) at the time of the subject visit or when the assessment is performed (e.g., central wound rating group qualitative image review). Data already located in the subject's medical chart (medical history, medications, laboratory results) or data collected by study personnel untrained on the use of the EDC may be transcribed into the eCRF. Source documents, such as the clinic chart, are to be maintained separately from the eCRF to allow data verification. Because of the potential for errors, inaccuracies, and illegibility in transcribing data into eCRFs, original documentation of transcribed study data must be maintained at the site.

Authorized personnel will verify data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue data queries to correct missing data or discrepancies found against the source within the EDC system. Data validation will consist of automated and manual edit checks that are created directly in the EDC system. Edit checks will be executed on all data points defined and documented by the study team and data management will be able to issue manual queries as needed to the eCRF. Study metrics will be reported from the EDC system.

Only authorized site personnel will be able to enter/modify/correct data in the eCRF. Once all data have been verified by the Sponsor or designee, the Investigator must electronically sign the eCRF; this responsibility may not be delegated to other study personnel.

Non-transcribed data entered into an applicable system will be validated with automated edit checks at the time of entry. Data entered into systems other than EDC require an authorized electronic signature at the time of record save and do not require verification.

9.3 ON-SITE AUDITS

During the course of the study and/or after study completion, one or more study sites may be audited by authorized representatives of the Sponsor. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with ICH GCP and relevant local regulations.

Additionally, the study may be inspected by the IRB/IEC or regulatory authorities. These inspections may take place at any time during or after completion of the study and are based on local regulations.

10 REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

10.1 GOOD CLINICAL PRACTICE

The procedures set out in this protocol are designed to ensure that the Sponsor and the Investigator abide by the principles of ICH GCP and the Declaration of Helsinki and applicable amendments. The study will also be conducted in accordance with applicable regional, national, and local regulatory and legal requirements.

10.2 INFORMED CONSENT

All subjects will be required to participate in the consent process. During the consent process, Investigator or designee obtaining consent will inform the subject of all elements of informed consent. No protocol-specific procedures, including screening procedures, will be performed until the subject has signed and dated an IRB/IEC-approved ICF. Study participation will start with the signing and dating of the ICF. A copy of the ICF will be provided to the subject for their records, and the original signed and dated ICF will be maintained in the source documentation files at the study site.

The Investigator must ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study. Subjects must also be notified that participation in the study is voluntary and that they are free to withdraw from the study at any time without prejudice to future care. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

In case of protocol amendment, the patient information leaflet (PIL)/subject information sheet and ICF may need to be revised to reflect the changes. If the PIL/subject information sheet and ICF are revised, they must be reviewed and approved by the responsible IRB/IEC and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

10.3 SUBJECT CONFIDENTIALITY AND DISCLOSURE

All study findings and documents will be regarded as confidential. The Investigator and members of his research team must not disclose such information without prior written approval from the Sponsor.

The Investigator must anonymize the data of the participating subjects. In this regard, the Sites and the Investigators shall be the unique parties with access to the personal data of the participating subjects. As a consequence, from a data protection approach, the Investigator and/or the Site acts as Data Controller of the personal data of the participating subjects and shall comply with all of its obligations under the General Data Protection Regulation, including obtaining the informed consent of the data subjects. The Investigator shall ensure that the data has been anonymized in accordance with the General Data Protection Regulation. The Sites and the Investigator shall also be responsible to comply with “HIPAA Privacy Rule” (which means the privacy rule issued under Health Insurance Portability and Accountability Act of 1996 and codified at 45 C.F.R. Parts 160 and 164).

The anonymity of participating subjects must be maintained. All subject data will be identified only by a subject ID number. Subject names and addresses must be maintained in a separate log. Documents that identify the subject (e.g., ICF) must be maintained in confidence by the Investigator.

However, in compliance with regulatory guidelines regarding the monitoring of clinical studies and in fulfilment of his/her obligations to the Sponsor, the Investigator must allow the study monitor, Sponsor representative or auditor, and/or IRB/IEC and relevant regulatory authority representatives access to the portion of the subject's medical record that is directly related to the study. The data to which the Sponsor representative or auditor would have access in this case will be anonymized at all times. Such information shall include all study-relevant documentation, including medical history to verify eligibility, admission/discharge summaries for hospital stays occurring while the subject is enrolled in the study, and autopsy reports if a death occurs during the study.

The anonymized data received by Sponsor may be subject to international transfers.

10.4 INDEPENDENT ETHICS COMMITTEE/ INSTITUTIONAL REVIEW BOARD APPROVALS AND NOTIFICATIONS

Before the start of the study, the protocol and other relevant documents will be approved by the IRB/IEC and relevant regulatory authorities in accordance with local regulatory requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study. The Investigator must conduct the study in compliance with the protocol.

Alterations to the protocol by the Sponsor will be documented in the form of a protocol amendment. Administrative changes may be made by the Sponsor without the need for a formal protocol amendment. All protocol amendments and administrative changes will be distributed by the Sponsor to all protocol recipients, with appropriate instructions.

The protocol amendments must be approved by the IRB/IEC and relevant regulatory authority prior to implementation (as appropriate) unless immediate implementation of the amendment is needed to eliminate a hazard to a subject or subjects.

During the course of the study, the Investigator should promptly inform the IRB/IEC of the following:

- Deviations from, or changes of, the protocol to eliminate immediate hazards to the study subjects
- Changes increasing the risk to subjects and/or affecting significantly the conduct of the study
- All adverse drug reactions that are both serious and unexpected
- New information that may affect adversely the safety of the subjects or the conduct of the study

- Study suspension or closure (Section 10.5)

If a safety issue of clinical relevance is identified, from review of any data, then the Sponsor will promptly notify the Investigator and relevant regulatory authorities, and the Investigator must inform the IRB/IEC of the safety issue as soon as possible after notification.

A safety issue of clinical relevance is one that has a relevant impact on the course of the study or program (including the potential for suspension of the study, program, or amendments to the protocol) or warrants immediate update of the PIL and ICF.

10.5 STUDY CLOSURE

The study may be temporarily suspended or prematurely terminated by the Sponsor at any time for any reason. Reasons for suspension or termination of the study may include, but are not limited to, determination of unacceptable risk to subject safety, noncompliance or insufficient data, or early determination of efficacy or futility. Written notification, documenting the reason for suspension/termination, will be provided to the Investigators and relevant regulatory authorities.

The Investigator must promptly notify the subjects and IRB/IEC of study completion or suspension/ET. In the event of suspension/ET, the notification should include the reason for the change in study status, and subjects must be contacted regarding any applicable changes to the study visit schedule.

The Investigator must submit eCRFs and all other relevant data and records to the Sponsor as soon as possible after the completion or ET of the study.

10.6 RECORD RETENTION

According to ICH GCP, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Sponsor will inform the Investigator when these documents no longer need to be retained.

11 STEERING COMMITTEE

A trial steering committee composed of academic nephrology, wound care and surgical experts, and dialysis care experts participated in the development of the protocol and will provide advice and guidance in the conduct and interpretation of the study and the presentation/publication of its results.

12 STUDY REPORT AND PUBLICATION POLICY

The aggregate results of the study will be documented by the Sponsor in the clinical study report for the purposes of regulatory submission.

By signing the protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. As appropriate, the regulatory authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

An Investigator shall not publish, or present for publication any articles or papers, or make any presentations, nor assist any other person in publishing any articles or papers, or making any presentations, or making any public declaration relating or referring to the study, the results of the study, in whole or in part, without the prior written consent of the Sponsor.

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APPENDIX 1. BATES-JENSEN WOUND ASSESSMENT TOOL (BWAT)

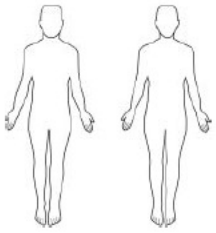
Sample paper collection form showing BWAT scoring. In this study, sites will be trained to score undermining, peripheral tissue edema, and peripheral tissue induration. A central wound rating group will rate the remaining BWAT items based upon review of the images (photos and videos) obtained by the site. Rating of the size item will be aided by automated measurements from the imaging software.

BATES-JENSEN WOUND ASSESSMENT TOOL

Complete the rating sheet to assess wound status. Evaluate each item by picking the response that best describes the wound and entering the score in the item score column for the appropriate date. If the wound has healed/resolved, score items 1,2,3, & 4 as =0.

Location: Anatomic site. Circle, identify right (**R**) or left (**L**) and use "X" to mark site on body diagrams:

____ Sacrum & coccyx ____ Lateral ankle
____ Trochanter ____ Medial ankle
____ Ischial tuberosity ____ Heel Other Site



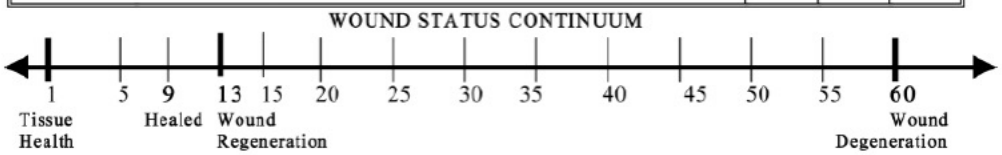
Shape: Overall wound pattern; assess by observing perimeter and depth.

Circle and date appropriate description:

____ Irregular ____ Linear or elongated
____ Round/oval ____ Bowl/boat
____ Square/rectangle ____ Butterfly Other Shape

Item	Assessment	Date Score	Date Score	Date Score
1. Size*	*0 = Healed, resolved wound 1 = Length x width <4 sq cm 2 = Length x width 4--<16 sq cm 3 = Length x width 16.1--<36 sq cm 4 = Length x width 36.1--<80 sq cm 5 = Length x width >80 sq cm			
2. Depth*	*0 = Healed, resolved wound 1 = Non-blanchable erythema on intact skin 2 = Partial thickness skin loss involving epidermis &/or dermis 3 = Full thickness skin loss involving damage or necrosis of subcutaneous tissue; may extend down to but not through underlying fascia; &/or mixed partial & full thickness &/or tissue layers obscured by granulation tissue 4 = Obscured by necrosis 5 = Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures			
3. Edges*	*0 = Healed, resolved wound 1 = Indistinct, diffuse, none clearly visible 2 = Distinct, outline clearly visible, attached, even with wound base 3 = Well-defined, not attached to wound base 4 = Well-defined, not attached to base, rolled under, thickened 5 = Well-defined, fibrotic, scarred or hyperkeratotic			
4. Under-mining*	*0 = Healed, resolved wound 1 = None present 2 =Undermining < 2 cm in any area 3 = Undermining 2-4 cm involving < 50% wound margins 4 = Undermining 2-4 cm involving > 50% wound margins 5 = Undermining > 4 cm or Tunneling in any area			
5. Necrotic Tissue Type	1 = None visible 2 = White/grey non-viable tissue &/or non-adherent yellow slough 3 = Loosely adherent yellow slough 4 = Adherent, soft, black eschar 5 = Firmly adherent, hard, black eschar			
6. Necrotic	1 = None visible 2 = < 25% of wound bed covered			

Item	Assessment	Date Score	Date Score	Date Score
Tissue Amount	3 = 25% to 50% of wound covered 4 = > 50% and < 75% of wound covered 5 = 75% to 100% of wound covered			
7. Exudate Type	1 = None 2 = Bloody 3 = Serosanguineous: thin, watery, pale red/pink 4 = Serous: thin, watery, clear 5 = Purulent: thin or thick, opaque, tan/yellow, with or without odor			
8. Exudate Amount	1 = None, dry wound 2 = Scant, wound moist but no observable exudate 3 = Small 4 = Moderate 5 = Large			
9. Skin Color Surrounding Wound	1 = Pink or normal for ethnic group 2 = Bright red &/or blanches to touch 3 = White or grey pallor or hypopigmented 4 = Dark red or purple &/or non-blanchable 5 = Black or hyperpigmented			
10. Peripheral Tissue Edema	1 = No swelling or edema 2 = Non-pitting edema extends <4 cm around wound 3 = Non-pitting edema extends >4 cm around wound 4 = Pitting edema extends < 4 cm around wound 5 = Crepitus and/or pitting edema extends >4 cm around wound			
11. Peripheral Tissue Induration	1 = None present 2 = Induration, < 2 cm around wound 3 = Induration 2-4 cm extending < 50% around wound 4 = Induration 2-4 cm extending > 50% around wound 5 = Induration > 4 cm in any area around wound			
12. Granulation Tissue	1 = Skin intact or partial thickness wound 2 = Bright, beefy red; 75% to 100% of wound filled &/or tissue overgrowth 3 = Bright, beefy red; < 75% & > 25% of wound filled 4 = Pink, &/or dull, dusky red &/or fills ≤ 25% of wound 5 = No granulation tissue present			
13. Epithelialization	1 = 100% wound covered, surface intact 2 = 75% to <100% wound covered &/or epithelial tissue extends >0.5cm into wound bed 3 = 50% to <75% wound covered &/or epithelial tissue extends to <0.5cm into wound bed 4 = 25% to < 50% wound covered 5 = < 25% wound covered			
	TOTAL SCORE			
	SIGNATURE			



Plot the total score on the Wound Status Continuum by putting an **"X"** on the line and the date beneath the line. Plot multiple scores with their dates to see-at-a-glance regeneration or degeneration of the wound.

APPENDIX 2. Wound-QoL Questionnaire

Wound-QoL questionnaire on quality of life with chronic wounds

The following questions are designed to find out how your chronic wound(s) affect(s) your quality of life.

Please check one box per line!

	In the last seven days ...	**not at all**	**a little**	**moderately**	**quite a lot**	**very much**
1	...my wound hurt	O	O	O	O	O
2	...my wound had a bad smell	O	O	O	O	O
3	...the discharge from the wound has upset me	O	O	O	O	O
4	...the wound has affected my sleep	O	O	O	O	O
5	...the treatment of the wound has been a burden to me	O	O	O	O	O
6	...the wound has made me unhappy	O	O	O	O	O
7	...I have felt frustrated because the wound is taking so long to heal	O	O	O	O	O
8	...I have worried about my wound	O	O	O	O	O
9	...I have been afraid of the wound getting worse or of getting new wounds	O	O	O	O	O
10	...I have been afraid of hitting the wound against something	O	O	O	O	O
11	...I have had trouble moving around because of the wound	O	O	O	O	O
12	...climbing stairs has been difficult because of the wound	O	O	O	O	O
13	...I have had trouble with everyday activities because of the wound	O	O	O	O	O
14	...the wound has limited my recreational activities	O	O	O	O	O
15	...the wound has forced me to limit my contact with other people	O	O	O	O	O
16	...I have felt dependent on help from others because of the wound	O	O	O	O	O
17	...the wound has been a financial burden to me	O	O	O	O	O

"Wound-QoL" questionnaire on Health-related Quality of Life in Chronic Wounds | Version English (US) | Augustin et al. 2014; Blome et al. 2014

APPENDIX 3. PROTOCOL AMENDMENT 1 - SUMMARY OF CHANGES

1) Revision of screening to a 2-step process (Screening Visit 1 and Screening Visit 2). CUA lesions will be evaluated at Screening Visit 2 to determine if there was significant healing since Screening Visit 1. Pain medications will be stabilized during the screening period. Holter monitoring and ECG will be conducted during Screening Visit 2. Subjects will be randomized at Screening Visit 2. SYNOPSIS, Table 1, Sections 3.1, 4.3, 5.1

2) Addition of Exclusion Criterion 15 specifying that subjects with significant improvement in their lesions between the first and second screening visit will be excluded. SYNOPSIS, Section 3.4.2

3) Addition of a pain medication diary in which subjects should record on a daily basis all pain medications taken. Site staff will review the diary with subjects at least weekly and record actual pain medications used in the eCRF. Average daily morphine milligram equivalents (MME) will be calculated centrally based on the information entered in the eCRF. SYNOPSIS, Table 1, Table 2, Sections 4.7.3.1, 4.7.3.2, 5.6.4

4) Revision of Inclusion Criterion 4 to increase the minimum score to 50 out of 100. SYNOPSIS, Section 3.4.1

5) Specification that the sites will be responsible for rating 3 BWAT components: undermining, peripheral tissue induration, and peripheral tissue edema. An expert central wound rating group will review the site's ratings and rate the remaining BWAT items based on review of the wound images (photos and video), aided by automated measurements from the imaging software for the wound size assessment. SYNOPSIS, Section 5.6.1.1

6) Addition of an external independent Data and Safety Monitoring Board. SYNOPSIS, Section 6.4

7) Addition of a secondary endpoint to assess the rate of change in opioid use from baseline to Week 12 as measured in MME. SYNOPSIS, Sections 8.1.1, 8.6.2

8) Addition of an exploratory endpoint to assess absolute change from baseline to Week 12 in opioid use as measured in MME. SYNOPSIS, Sections 8.1.1, 8.6.4

9) Processes for discontinuation from study drug and withdrawal from further follow-up are more clearly differentiated. Subjects who discontinue study drug early during Part 1 or Part 2 will be asked to complete study assessments throughout the respective part of the study (Part 1 or Part 2) and complete a follow-up visit. Subjects who discontinue study drug and are unwilling to complete the remaining study assessments will be encouraged to return for an early termination visit 4 weeks after the last dose of study drug. SYNOPSIS, Table 1, Table 2, Sections 3.1, 5.4, 7

10) Specification that the Pain VAS will be in reference to the subject's *worst* wound-related pain during the previous 24 hours. SYNOPSIS, Section 5.6.2

11) Specification that local ECGs will be obtained using the ECG instrument that will be supplied with the Holter monitor. Clarification of the recording window and timepoints for screening and dosing days. Table 1, Table 2, Section 5.8.5

12) Specification that ionized calcium samples must be shipped on day of collection under ambient conditions. Table 1, Table 2, Section 5.8.6

13) Specification that dialysis parameters to be collected include calcium concentration in the dialysate, dialysis frequency and duration, and Kt/V or URR. Estimated Kt/V or URR from the dialysis machine or calculated values using local lab measurements may be collected but the same measure and same data source must be used throughout the study. Table 1, Table 2, Section 4.7.3.4

14) Clarification of the distinction between hemodialysis-related events and adverse events. Table 1, Table 2, Section 8.9.2

15) Specification that blinding to the treatment assignment for Part 1 will be maintained for the duration of the study including Part 2 and follow-up until the study database is locked. This applies to the Investigator, site staff, subjects, central wound rating group, central Holter/ECG readers, and Sponsor staff (including designees) involved in the conduct of the study and data management. Sections 4.4.1, 5.6.1.2, 8.9.4

16) Clarification that background care for CUA includes wound care, dialysis parameters (calcium concentration in the dialysate, dialysis frequency and duration), pain medications, and other concomitant medications relevant to the management of CUA. Section 4.7.3

17) The processes for stabilizing pain medications during screening and maintenance of pain management during the trial are provided. Sections 4.7.3.1, 4.7.3.2

18) The types of wound care to be collected are provided. Section 4.7.3.3

19) The order of assessments is clarified. Section 5.5

20) Additional details on the sample size re-estimation are provided. Section 8.2.2

21) Details on how missing data will be handled under the assumption of missing not at random. Section 8.6.1

22) Additional minor formatting and clarifications throughout.

APPENDIX 4. PROTOCOL AMENDMENT 2 - SUMMARY OF CHANGES

1) Protocol Agreement Page: Administrative update to the Sponsor signatory.

2) SYNOPSIS and Section 3.4 Study Population: Increased the number of study sites to "approximately 60".

3) SYNOPSIS and Section 5.6.1 Wound Evaluation:

    a. Added the specification that the central reviewers will be unaware of the order of the visits when completing BWAT ratings and qualitative review.

    b. Central BWAT raters will perform a quality review of the site's ratings.

    c. Qualitative review of wound healing will be conducted only for the primary lesion.

4) SYNOPSIS and Section 8.1.1 Efficacy Endpoints: Added the Wound-QoL subscales to the exploratory endpoints.

5) Table 1. Schedule of Events for Part 1. Footnote 14: Added the specification that the sample for the serum pregnancy test must be drawn within 7 days prior to the first dose of study drug.

6) Table 1. Schedule of Events for Part 1 and Section 5.1 Screening Period: Clarified that randomization may occur up to one week prior to Week 1 Day 1 rather than on Week 1 Day 1.

7) Table 1. Schedule of Events for Part 1: Removed "pre-dose and EOI" from the ECG row because there is no study drug dose during screening. Timing of the local ECGs is specified in footnote 10. Removed ECG assessment at Week 6.

8) Table 1. Schedule of Events for Part 1 Footnote 10 and Table 2. Schedule of Events for Part 2 and Follow-Up Footnote 8, and Section 5.8.5 Holter Monitoring and Electrocardiograms: Adjusted the collection window for the EOI local ECG to within 20 minutes prior to EOI.

9) Table 1. Schedule of Events for Part 1 and Table 2. Schedule of Events for Part 2 and Follow-Up and Section 5.5 Order of Assessments and Section 5.8.5 Holter Monitoring and Electrocardiograms: Specified that the Holter monitor will be placed on the subject 30 min prior to the beginning of dialysis and that the recording window will be from that time until the end of dialysis.

10) Table 1. Schedule of Events for Part 1: Removed indicator in the table for New CUA Lesion Assessment at Week 1 Day 1 because a new lesion is defined as one that has occurred since Week 1 Day 1 (as defined in Section 5.6.1.3).

11) Table 1. Schedule of Events for Part 1 Footnotes 11 and 19 and Table 2. Schedule of Events for Part 2 and Follow-Up Footnotes 9, 17, and 18 and Section 5.7 PK, PD, and Biomarkers and Section 5.8.6 Laboratory Evaluations: Adjusted the collection window for the EOI samples to within 20 minutes prior to EOI.

12) Section 1.1.1 Calciphylaxis: Updated description of typical lesion locations to "Lesions most commonly appear in the lower extremities and in the trunk, particularly in the abdomen. Less commonly reported locations include the arms, hands and fingers, buttock/hip, chest, and genitals."

13) Section 1.4 Clinical Experience: Added relevant results from completed Study SNFCT2015-05.

14) Section 1.6 Risk-Benefit Assessment: New section summarizing risk-benefit assessment.

15) Section 3.1 Study Design Overview: Added definitions of subject study completion and end of study.

16) Section 3.2 Discussion of Study Design: Clarified the CUA diagnosis will be made by the Investigator with confirmation from the central wound rating group based on review of images of the primary lesion. Biopsy results will not be collected.

17) Section 4.4.2 Unblinding: Removed the requirement that the Investigator consult with the Medical Monitor prior to unblinding and removed the requirement for a subject to be discontinued from study drug if the subject's treatment is unblinded.

18) Figure 2. Method of Study Drug Administration: Replaced figure with an improved schematic. Note, there are no changes in the method of study drug administration.

19) Section 4.7.3.1 Stabilizing Pain Medications: Added that subjects should be instructed to bring the pain medication diary with them to the site at each visit.

20) Section 4.7.4.2 Contraception Requirements:

    a. Added the specification that abstinence is acceptable only as defined as true abstinence in line with the preferred and usual lifestyle of the subject.

    b. Further clarified what methods of contraception are not acceptable.

    c. Specified that male subjects should adhere to the contraception requirements from screening through 30 days after the last dose of study drug.

21) Section 5.1. Screening Period: Due to visit scheduling, a subject's Week 1 Day 1 visit may occur up to 7 days after randomization. Added the specification that the Medical Monitor should be consulted if the Investigator observes changes to the primary lesion (e.g., significant improvement from screening) or changes to the subject's clinical

condition which may make the subject ineligible during the time between randomization and Week 1 Day 1.

22) Table 4. Holter Instructions and Timing: New table with additional instructions added for clarity.

23) Table 5. Local ECG Tracing Collection Timepoints: New table with additional instructions added for clarity.

24) Section 7.1 Discontinuation of Study Drug and Section 7.2 Withdrawal of Subject from the Study: Added the specification that a subject should be discontinued from study drug if they experience a CTCAE Grade 4 adverse event that is considered by the Investigator to be related to the study drug and not due to comorbidities or the disease.

25) Section 13 References: Section updated.

26) Appendix 3: The summary of changes from the previous version of the protocol (Amendment 1) has been moved to an appendix.

27) Minor changes for clarity and revisions of amendment number and date throughout.