CALCIPHYX

Title	**Statistical Analysis Plan**
Version Number	1.3
Date	10 APR 2023
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	SNFCT2017-06
Sponsor	Sanifit Therapeutics SA
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Approvals

Name and Role	Signature and Date
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SAP Version 1.3 – Summary of Changes from Version 1.2

Section 6.3 Retests, Unscheduled Visits and Early Termination Data

Description of handling of unscheduled measurements had been inadvertently omitted and has been added. Unscheduled measurements will be assigned to the nearest scheduled visit. If a measurement does not fall into a specified visit window, then that measure will be listed only and will be excluded from data summaries and analyses.

Section 6.6 Multiple Wound Images

This new section describes determination of BWAT score, wound area, and qualitative review when greater than one photo was required to image a wound.

Section 9 Disposition and Withdrawals

An incomplete sentence has been corrected.

Section 15.1.2. Primary Analysis of Primary Efficacy Variables

- An error has been corrected in the description of the MMRM model for the Pain VAS alternate primary endpoint. The inclusion of pain medication use at each time point was stated in error and has been deleted.
- An error has been corrected for the confidence level for Pain VAS difference in LS means.

SAP Version 1.2 – Summary of Changes from Version 1.1

1) Section 7.4 Multiple Comparisons/ Multiplicity. The formulas to compute the final analysis *z* values were corrected to properly reflect that the square root of the weights should be used.

SAP Version 1.1 – Summary of Changes from Version 1.0

1) Section 6.2 Baseline. Additional details are provided on handling of missing baseline values. Unless otherwise specified, if the assessment is missing, the last pre-dose assessment will be assigned as baseline. For Pain VAS, missing baseline data will be imputed with the lower of these two values: that subject's last pre-dose Pain VAS value OR the mean baseline Pain VAS value among subjects in the same treatment arm.

2) Section 15.1.2 Primary Analysis of Primary Efficacy Variables. An error has been corrected in the description on the MMRM model. The "Week 1 Day 1" value has been deleted from the list of fixed effect terms.

3) Section 15.1.3.3 Sensitivity Analyses with Regard to Pain Medication Use Over Time. An error has been corrected in the description of the random coefficient MMRM model. "Week 0" has been deleted from the list of visits.

4) Section 15.2.1.3 Qualitative Wound Image Evaluation for the Primary Lesion. An error has been corrected in the longitudinal logistic regression model description. "Week 1 Day 1" value has been deleted from the list of predictors.

5) Section 15.1.3.2 Sensitivity Analyses with Regard to Missing Baseline Primary Endpoint Data. A sensitivity analysis has been added in which the primary analyses of BWAT and Pain VAS are repeated without imputation of missing baseline values.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ATC	Anatomical Therapeutic Chemical
BLQ	below the lower limit of quantification
BMI	body mass index
BWAT	Bates-Jensen Wound Assessment Tool
BWAT-CUA	Bates-Jensen Wound Assessment Tool – Calcific Uremic Arteriolopathy
CI	confidence interval
CP	conditional power
CRF	case report form
CRO	contract research organization
CUA	calcific uremic arteriolopathy
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
EOI	end of infusion
GEE	generalized estimating equation
HD	hemodialysis
hs-CRP	high-sensitivity C-reactive protein
IDDI	International Drug Development Institute
Kt/V	clearance time / volume
LS	least squares
MAR	missing at random
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mITT	modified intent-to-treat
MME	morphine milligram equivalent
MMRM	mixed model for repeated measures
MNAR	missing not at random
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamic
PK	pharmacokinetic
PMM	Pattern-Mixture Model
PP	per protocol
PT	preferred term
PTH	parathyroid hormone
QoL	quality of life
SAE	serious adverse event

SAP	statistical analysis plan
SI	International System of Units
SOC	system organ class
SSRE	sample size re-estimation
STS	sodium thiosulfate
TEAE	treatment emergent adverse event
TIW	three times in a week
ULQ	upper limit of quantification
URR	urea reduction ratio
VAS	visual analog score
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Study SNFCT2017-06. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed and is based on protocol Amendment 2 version, dated 21 MAY 2021.

2. STUDY DESIGN

2.1. General Description

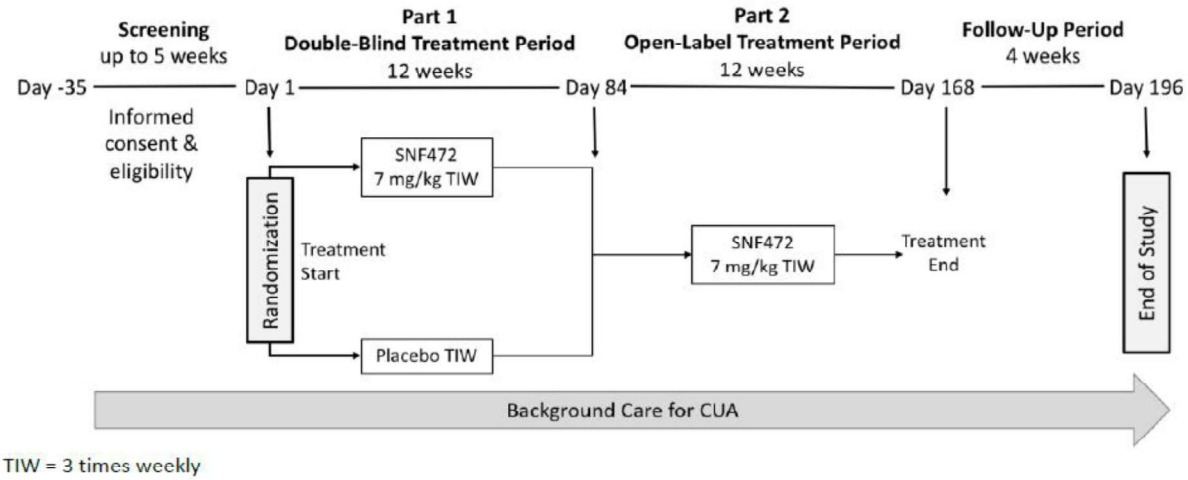
This Phase 3, global multicenter study will examine the efficacy and safety of SNF472 in adult subjects on maintenance hemodialysis (HD) who have at least one ulcerated calcific uremic arteriolopathy (CUA) lesion. CUA is also referred to as "calciphylaxis."

The sample size is 66 subjects across approximately 60 worldwide sites, with a potential adjustment to 99 subjects with the sample size re-estimation (SSRE) procedure planned when primary endpoint data are available from approximately 33 of the planned total of 66 subjects randomized and treated for 12 weeks.

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.

A study flow chart is provided in Figure 1.

Figure 1: Study Design Flowchart



2.2. Schedule of Events

Schedule of events can be found in Table 1 and Table 2 of the protocol.

2.3. Sample Size

The sample size calculation is based on the effect sizes and standard deviations (SD) observed for changes in the Bates-Jensen Wound Assessment Tool – Calcific Uremic Arteriolopathy (BWAT-CUA) and Pain Visual Analog Score (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 $\rho = 0.90$ to 0) when the alternate primary endpoints are tested using a Hochberg closed test procedure with a 4% alpha level, 2 sided.

3. STUDY OBJECTIVES

The study objectives 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.

3.1. Primary Endpoints

The primary alternate efficacy endpoints are:

- 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

3.2. Secondary Endpoints

The secondary efficacy endpoints evaluated hierarchically are:

- Absolute change from baseline to Week 12 in Wound-Quality of Life (Wound-QoL) score
- Absolute change from baseline to Week 12 in the BWAT total score for 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

3.3. Exploratory Endpoints

The exploratory efficacy endpoints are:

- 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 baseline to 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

3.4. Safety Endpoints

The safety endpoints are:

- Proportion of subjects with Treatment-Emergent and Treatment-Related adverse events (AEs), serious AEs (SAEs) and deaths

- Change from baseline in the following:
  - Laboratory parameters
  - Holter monitoring results
  - QTc interval and other electrocardiogram (ECG) parameters
  - Vital signs
- Proportion of subjects with a CUA wound-related infections, sepsis, hospitalization or any CUA wound-related complication.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Interim analysis for sample size re-estimation (SSRE) will be prepared by an independent International Drug Development Institute (IDDI) Biostatistics team
- Final Analysis

4.1. Interim Analysis for Sample Size Re-estimation (SSRE)

The SSRE is planned when primary endpoint data are available from approximately 33 of the planned total of 66 subjects randomized and treated for 12 weeks. 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 + ½ × 66=99 subjects).

The IDDI study team, including those responsible for creating the programs to produce the outputs for the SSRE, will remain blinded. Once the programs have been produced by the IDDI study team, these programs will be sent to an independent statistician, who will confirm the process and programming. Upon approval, IDDI will have an unblinded statistician not associated with the trial conduct the randomization schedule and provide the conditional power and sample size computations to the Data and Safety Monitoring Board (DSMB).

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 1 gives the decision rule with regards to continuation of the study with or without a sample size increase.

The CP computed as above 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 1. 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_2will 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 (z_{11} and z_{12}, say, for the first primary endpoint and z_{21} and z_{22}, say, for the second primary endpoint) using NOT the approach suggested by Mehta and Pocock (2011), but rather the approach defined by Cui (1999), Equation 3.3 and later generalization, which guarantees no alpha inflation regardless of how the post-interim sample sizes (i.e., $\tilde{n}_1$ and $\tilde{n}_2$) are determined.

Table 1: Decision Rules for Sample Size Increase

Conditional Power		BWAT-CUA			
		< 10%	≥ 10% - <30%	≥ 30% - < 90%	≥ 90%
Pain 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

SS=sample size; VAS=visual analog score

The Sponsor will receive only the sample size recommendation from the DSMB, not the conditional power assessments. Finally, the Sponsor retains full discretion with regards to the outcome of the SSRE procedure and may decide to continue the trial with the sample size increased as described above or unchanged.

No inflation of the Type 1 error is expected with the proposed method and therefore no adjustment for the overall alpha is required.

4.2. Final Analysis

All final, planned analyses identified in this SAP will be performed by IDDI Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Approval for Database Lock by the Clinical contract research organization (CRO), Sponsor Authorization of Analysis Sets and Unblinding of Treatment.

IDDI Biostatistics will not be performing any pharmacokinetic (PK)/pharmacodynamic (PD) analyses or extracted ECG analysis and this SAP does not contain any details relating to PK or PD parameters or analyses.

5. ANALYSIS POPULATIONS

5.1. Enrolled Population

The Enrolled Population will contain all subjects who provide informed consent and are screened eligible for this study.

5.2. Randomized Population

The Randomized Population will contain all subjects in the Enrolled Population who were randomized to study drug. For analyses and displays based on the Randomized Population, subjects will be classified according to randomized treatment without regard to whether the assigned treatment was administered or not.

5.3. Safety Analysis Population

The safety analysis population will contain all subjects in the Randomized Population who receive at least one dose of study drug and subjects will be analyzed according to treatment received in Part 1 (i.e., for Part 2, subjects who were on placebo and subjects who were on SNF472 in Part 1 will be analyzed separately in Part 2). The safety population will be used for analyses of safety endpoints. If there is any doubt whether a subject was treated or not, they will be assumed treated for the purposes of analysis. Any patient who receives at least one dose of SNF472 will be considered as treated with SNF472 for safety purposes.

5.4. Modified Intent-to-Treat Population (mITT)

The modified intent-to-treat (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. Efficacy evaluations include the BWAT-CUA score from Central Wound Rating, Pain VAS score, Wound-QoL score, BWAT total score, qualitative wound image evaluation, and opioid use. Subjects will be analyzed according to the treatment to which they were randomized. The mITT population will be the primary analysis population for efficacy endpoints.

5.5. Intent-to-Treat Population (ITT)

The intent-to-treat (ITT) population will consist of all enrolled subjects who are randomized. Supportive analyses of the two alternate primary endpoints BWAT-CUA score from Central Wound Rating and Pain VAS score, will be performed in this population. Subjects will be analyzed according to the treatment to which they were randomized.

5.6. Per Protocol Population (PP)

The per-protocol (PP) population will be the subset of subjects in the mITT population who do not have any major protocol deviations that will impact the efficacy assessment, have a Week 12 measurement of at least one of the primary efficacy variables, and have received a pre-specified minimum study drug exposure. Protocol deviations will be reviewed prior to unblinding to determine whether they are cause for exclusion of a subject from the Per Protocol population. This review will be fully blinded and without reference to efficacy or other data.

The PP population will be used for supportive analyses of efficacy endpoints.

6. GENERAL CONSIDERATIONS

6.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to derive start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of study drug; for subjects in Part 1, the reference start date is Week 1 Day 1; for subjects in Part 2 who were on placebo in Part 1, their reference start dates will be: reference start date 1 which is Week 1 Day 1 and reference start date 2 which is Week 13 Day 1. Study day will appear in every listing where an assessment date or event date appears. It is calculated as the difference between the event date and the reference start date.

- If the date of the event is on or after the reference start date, then:

  Study Day = (date of event – reference start date) + 1

- If the date of the event is prior to the reference start date, then:

  Study Day = (date of event – reference start date)

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings.

6.2. Baseline

Unless otherwise specified, baseline is defined as the Week 1 Day 1 pre-dose assessment. For BWAT and other endpoints except Pain VAS, if the assessment is missing, the last pre-dose assessment will be assigned as baseline. For Pain VAS, missing baseline data will be imputed with the lower of these two values: that subject's last pre-dose Pain VAS value OR the mean baseline Pain VAS value among subjects in the same treatment arm. In the case where the date of assessment and the reference start date coincide, collection time, where available will be compared. The measurement will be considered pre-baseline unless the measurements were taken post-dialysis according to the schedule of events, such as vital signs, and the AEs and medications commencing on the reference start date will be considered post-baseline.

6.3. Retests, Unscheduled Visits and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will be assigned to the nearest scheduled visit as per Table 2 (Part 1) and Table 3 (Part 2), and will be fully listed by subject and nominal visit. If a measurement does not fall into a specified visit window, then that measure will be listed only and will be excluded from data summaries and analyses. When there are multiple measures falling into a given visit window, the non-missing measure closest to the nominal visit time point will be used in data summaries and analyses. All values within a visit window will contribute to the assessment of best/worst case value where required (e.g., shift table).

In the case of a retest (same visit number assigned), the earliest available measurement for that visit will be used for by-visit summaries.

Table 2: Visit Windows Part 1

Measurement Frequency/Endpoints	Planned Visit	Starting Hour/Day for Visit Window	Ending Hour/Day for Visit Window
--	Baseline Part 1	See Section 6 2	See Section 6 2
Weekly Day 3 and Week 12 Day 5	Week 2/Day 3	> 0 hr Week 1 Day 1	≤23:59 hr of Week 2 Day 7
	Week x/Day 3 $x = 3, 4, \ldots, 11$	> 0 hr Week x Day 1	≤23:59 hr of Week x Day 7
	Week 12/Day 5	> 0 hr Week 12 Day 1	≤23:59 hr of Week 12 Day 7 and before first dosing date and time of Part 2
Week 6 Day 3 and Week 12 Day 5	Week 6/Day 3	> 0 hr Week 4 Day 3	≤23:59 hr of Week 8 Day 3
	Week 12/Day 5	> 0 hr Week 10 Day 5	Before first dosing date and time of Part 2
Biweekly Day 3 and Week 12 Day 5	Week 2/Day 3	> 0 hr Week 1 Day 1	≤23:59 hr of Week 3 Day 2
	Week x/Day 3 $x = 4,6,8$ and 10	> 0 hr Week $x - 1$ Day 3	≤23:59 hr of Week $x + 1$ Day 2
	Week 12/Day 5	> 0 hr Week 11 Day 3	Before first dosing date and time of Part 2

Table 3: Visit Windows Part 2

Measurement Frequency	Planned Visit	Starting Hour/Day for Visit Window	Ending Hour/Day for Visit Window
--	Baseline Part 2 (only applicable for parameters not measured at Week 13 Day 1)	Use date and time for Week 12 Day 5 in the Part 1 table (Table 2)	Use date and time for Week 12 Day 5 in the Part 1 table (Table 3)
--	Week 13 Day 1 (only applicable for parameters measured at Week 13 Day 1)	> 0 hr Week 13 Day 1	≤23:59 hr of Week 13 Day 1
Weekly Day 3 and Week 24 Day 5	Week 14/Day 3	> 0 hr Week 13 Day 1	≤23:59 hr of Week 14 Day 7
	Week x/Day 3 $x = 15, 16, \ldots, 23$	> 0 hr Week x Day 1	≤23:59 hr of Week x Day 7
	Week 24/Day 5	> 0 hr Week 24 Day 1	≤23:59 hr of Week 24 Day 7
Week 18 Day 3 and Week 24 Day 5	Week 18/Day 3	> 0 hr Week 16 Day 3	≤23:59 hr of Week 20 Day 3
	Week 24/Day 5	> 0 hr Week 22 Day 5	≤23:59 hr of Week 26 Day 5
Biweekly Day 3 and Week 24 Day 5	Week 14/Day 3	> 0 hr Week 13 Day 1	≤23:59 hr of Week 15 Day 2
	Week x/Day 3 $x = 16,18,20$ and 22	> 0 hr Week $x - 1$ Day 3	≤23:59 hr of Week $x + 1$ Day 2
	Week 24/Day 5	> 0 hr Week 23 Day 3	≤23:59 hr of Week 25 Day 5

Early termination data will be mapped to the next available visit number for by-visit summaries. Subjects completing the study should return for a follow-up visit 4 weeks after the last dose of study drug; for such follow-up assessments, a window of + 2 weeks will be applied.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. Statistical Tests

The default significant level will be 5% with the alternate primary endpoints to be tested at a 2-sided alpha level of 4% using a Hochberg procedure while the secondary endpoints will be tested at either 5% (if both primary endpoints are met) or 1% (if only one of the two primary endpoints is met), thus protecting the overall type I error. Confidence intervals (CIs) will be 96% 2-sided for the alternate primary endpoints if both are met; if only one alternate primary is met, a 98% 2-sided CI will also be presented for that alternate primary. With respect to secondary endpoints, if both primary endpoints are met, CIs will be 95% 2-sided for all secondary endpoints whereas if only one of the two primary endpoints is met, CIs will be 99% 2-sided for secondary endpoints. Otherwise, all CIs will be 95% 2-sided and all tests will be made at the 5% level be two-sided, unless specified differently in the description of the analyses.

In terms of the effect of the SSRE interim analysis on the validity of the estimate and confidence interval for the treatment effect with the combined data under the SSRE scheme, there is no issue that will affect these estimates. In computing valid point and interval estimates in the final analysis, these estimates will follow standard procedures since (i) the interim is only to reassess sample size, so there is no possibility to stop early for efficacy; and (ii) the Cui (1999) approach used to combine pre- and post-interim data guarantees no increase in type I error. Hence there

is no issue related to the point or interval estimation in the final analysis using the approach described above in Section 4.1.

6.5. Common Calculations

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

6.6. Multiple Wound Images

In the instance where a single wound is large and must be imaged with greater than one photo, BWAT item scores will be calculated as the mean of the BWAT item scores for each of the images for a visit. Wound area will be calculated as the sum of the areas determined for each of the images for a visit. A qualitative review response will be determined by the mode of responses. If there is an equal number of different qualitative response types, the worst response will be used.

6.7. Software Version

All analyses will be conducted using SAS version 9.4 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. Adjustments for Covariates and Factors to be Included in Analyses

The following covariates and factors are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Factor 1: Sodium thiosulfate (STS, any formulation) use at baseline (Yes/No)
- Factor 2: Treatment
- Factor 3: Visit
- Factor 4: Visit by Treatment interaction
- Covariate 1: BWAT-CUA baseline score
- Covariate 2: Pain VAS baseline score
- Covariate 3: Wound – Quality of Life (Wound-QoL) baseline score
- Covariate 4: BWAT total baseline score

7.2. Multicenter Studies

This study will be conducted by multiple investigators at multiple centers internationally. Randomization to treatment arms is not stratified by country/center.

When specified, statistical analysis will be adjusted for geographic region. Geographic region will be categorized as follows:

Geographic Region	Country
North America	United States
Europe	UK, Spain, Italy, Belgium, Germany, Poland

Center pooling will not be carried out for use in analyses for this study.

7.3. Missing data

Missing safety and efficacy data will be handled as described in Sections 15 and 16 of this SAP.

7.4. Multiple Comparisons/ Multiplicity

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.

In terms of incorporation of the interim analysis for SSRE (Section 4.1) into the Hochberg procedure to control overall Type I error, the Hochberg procedure will simply be applied to the combined z-values in the final analysis; if N represents the originally planned overall study sample size and the interim for sample size reassessment is to be performed with n subjects, then the final analysis z values for the two primary endpoints, z_1 and z_2, say, $\left(\text{where } z_1 = \sqrt{\left(\frac{n}{N}\right)}\, z_{11} + \sqrt{\left(\frac{N-n}{N}\right)}\, z_{12} \text{ and } z_2 = \sqrt{\left(\frac{n}{N}\right)}\, z_{21} + \sqrt{\left(\frac{N-n}{N}\right)}\, z_{22}\right)$ will be assessed via the Hochberg procedure.

7.5. Examination of Subgroups

Subgroup analyses will be conducted as stated in the exploratory analysis sections. It should be noted that the study was not designed to detect treatment differences with statistical power within subgroups.

The following subgroups may be assessed for the primary and secondary endpoints:

- Sex:
  - Female
  - Male
- Age (years):
  - ≥18 to ≤44
  - ≥45 to ≤64

  - ≥65 to ≤74
  - ≥75
- Race in groups:
  - Black/African American
  - Asian
  - Native Hawaiian/Other Pacific Islanders
  - American Indian/Alaska Native
  - White
  - Other
  - More than one
- Region:
  - North America
  - Europe
- Major comorbid conditions:
  - Diabetes mellitus (Yes/No)
  - Peripheral vascular disease (Yes/No)
  - Obesity (BMI > 30) (Yes/No)
  - Time on Dialysis (years:months)
- Medication use at baseline
  - STS (Yes/No)
  - Calcimimetic (Yes/No)
  - Noncalcium-based phosphate binder (Yes/No)
  - Calcium-based phosphate binder (Yes/No)
  - Warfarin (Yes/No)
  - Vitamin K compound (Yes/No)
  - Vitamin D compound (Yes/No)
  - Opioids (Yes/No)

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IDDI Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition and withdrawals will be presented in a CONSORT diagram with footnotes as needed. Protocol deviations will be presented for the Randomized Population and outputs including inclusion and exclusion criteria for all subjects in the Enrolled Population will be provided.

The number and percentage of subjects in each of the disposition categories will be summarized. For the End of Treatment and End of Study, subjects who have completed treatment for Part 1, continued into Part 2, completed treatment for Part 2, discontinued treatment in Part 1, discontinued treatment in Part 2, completed the study and reason for discontinuation will be summarized. A subject disposition listing including subjects who discontinued treatment and/or study early will be provided along with the reasons for discontinuations. The disposition will differentiate patients who: (1) had early cessation of therapy by physician/study staff; (2) were lost to follow-up; and (3) patients who withdrew consent for follow-up.

The reasons for discontinuations include:

- Adverse event
- Lost to follow up
- Pregnancy
- Study terminated by sponsor
- Withdrawal by subject
- Physician decision
- Death
- Other

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the Randomized, Safety, and mITT Populations.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) categorical based on subgroups:
  - ≥18 to ≤44
  - ≥45 to ≤64
  - ≥65 to ≤74
  - ≥75
- Age (years) continuous
- Major comorbid conditions

  - Diabetes mellitus (Yes/No)
  - Peripheral vascular disease (Yes/No)
  - Hypoalbuminemia (Yes/No)
  - Obesity (BMI>30)(Yes/No)
  - Time on Dialysis (Years:months)
  - Hyperphosphatemia
- Pain medication use at baseline
  - Opioids
  - NSAIDs
  - Anticonvulsants
  - Anesthetics
  - Other pain medications
- Other medication use at baseline
  - STS (Yes/No)
  - Calcimimetic (Yes/No)
  - Noncalcium-based phosphate binder (Yes/No)
  - Calcium-based phosphate binder (Yes/No)
  - Warfarin (Yes/No)
  - Vitamin K compound (Yes/No)
  - Vitamin D compound (Yes/No)
- Sex
- Ethnicity
- Race
- Weight (kg)
- Height (cm)
- BMI (kg/m^2) continuous
- BMI (kg/m^2) categorical (underweight, normal, overweight, obese)
- Time since diagnosis (years) of end stage renal disease - calculated relative to date of consent
- BWAT-CUA score
- BWAT total score
- Pain-VAS score
- Wound-QoL score

10.1. Derivations

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$

11. PROCEDURE AND MEDICAL HISTORY

Procedure and Medical History information will be presented for the Safety Analysis Population.

- Medical and Procedure History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 23.1 or later.
  - Data captured on the Medical and Procedure History page of the case report form (CRF) will be presented by System Organ Class (SOC) and Preferred Term (PT).

12. MEDICATIONS

Medications will be presented for the safety population and coded using WHO Drug Dictionary Global Version September 2020 and summarized by Part 1 (prior and concomitant), Part 2 (concomitant only) and overall. To distinguish between Parts 1 and 2, the medication start date will be used relative to subject's start date in Part 1 and Part 2.

Anatomical Therapeutic Chemical (ATC) class coding will be performed, and the medications will be summarized under the ATC Level 1 and 4 coding.

See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior and concomitant, the medication will be classified by the worst case, i.e., concomitant.

- 'Prior' medications are medications which started and stopped prior to the first dose of study drug and those that were taken during the past 30 days prior to the first dose of the study will be flagged.
- 'Concomitant' medications are medications which started prior to, on or after the first dose of study drug which is Week 1 Day 1 and continues to be used during the trial.

13. STUDY DRUG EXPOSURE

Exposure to study drug in days will be summarized for the safety population. The summary will be for Part 1 subjects who were on a study drug and overall for both Parts 1 and 2.

The date of first study drug administration will be taken from the eCRF "Study Drug Administration" form. The earliest start date of study drug infusion where the subject was dosed will be considered the date of first study drug administration. The date of last study drug will be taken from the eCRF "End of Study Treatment" form. Interruptions (including

hospitalizations when it may not be possible to administer study drug) and compliance are not considered for duration of exposure.

13.1. Derivations

Duration of exposure (days) = date of last study drug administration – date of first study drug administration + 1.

13.2. Exposure

The planned dose of SNF472 (7 mg/kg) will be administered three times weekly during dialysis in the Parts 1 and 2 of the trial.

Compliance (number of doses administered/number of doses scheduled based on the duration of the subject's participation) will be categorized as follows: 0-20%, >20-40%, >40-60%, >60-80%, >80-100%, >100-120%. Compliance categories will be summarized with descriptive statistics by treatment group and overall in the mITT population. The number of doses scheduled will assume a week consisting of 2 days expect 1 dose, a week consisting of 4 days expect 2 doses, and a week of 5 days expect 3 doses. 100% compliance over 52 weeks consists of 156 doses.

Any infusion interruptions, stopped infusions, missed infusions, discontinuations, and duration/number of infusions will be summarized for Part 1 and Part 2 separately, by visit (as listed on the Study Drug Administration "Visit" CRF page).

14. STUDY DRUG COMPLIANCE

Compliance to study drug will be presented for the safety population.

The listing by subjects of planned and actual doses will be presented.

The compliance will be 100% if the actual dose is equal to the planned dose. In case the two are not equal, the compliance will be calculated as (actual/planned)*100. The compliance will be presented for each part of the study separately across all subjects.

15. EFFICACY OUTCOMES

15.1. Primary Efficacy

15.1.1. Primary Efficacy Variables & Derivations

Primary efficacy analyses will be performed using the mITT population, and supportive analyses, using the ITT and PP populations.

There are two alternate primary efficacy variables:

The first primary efficacy variable is absolute change from baseline to Week 12 in the BWAT-CUA score for the primary lesion. The BWAT-CUA score focuses on the 8 prototypical features

of CUA lesions which are 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 is rated on a scale of 1 representing 'best' to 5 representing 'worst'. The sum of these scores is 8 to 40 which is the possible range of scores for BWAT-CUA. For the missing assessments on any one of the BWAT-CUA items when the other items are present, the scores will be imputed by using the median of available scores for a particular item within the given randomized treatment group at that visit. A sensitivity analysis will also be performed by imputing missing assessments on any one of the BWAT-CUA items with a worst-case score of '5'.

The second primary efficacy variable is absolute change from baseline to Week 12 in Pain VAS score. The Pain VAS will be electronically administered, requiring the subject to mark a position on a 10-cm (100-mm) long horizontal line to indicate his/her worst wound-related pain over the last 24 hours. From this mark, the VAS score is electronically recorded in mm based on measurement along the line. The Pain VAS score is collected in the raw data in the CRF.

15.1.2. Primary Analysis of Primary Efficacy Variables

The comparison of absolute change from baseline to Week 12 in BWAT-CUA score between treatment groups will be achieved using a MMRM analysis to estimate the difference between randomized treatment groups least squares means (LS means) at 12 weeks. The model will include fixed effect terms for randomized treatment, visit (Week 2 Day 3, Week 4 Day 3, Week 6 Day 3, Week 8 Day 3, Week 10 Day 3 and Week 12 Day 5) and visit by randomized treatment interaction; the model will also include baseline STS use as a fixed effect and baseline BWAT-CUA score will be included as a covariate. Subject will be fitted as random effect and an unstructured variance-covariance matrix will be used. In case the unstructured variance-covariance results in the lack of convergence, the following covariance structures will be tried in order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, and autoregressive. The difference in least square means (LS Means) with corresponding confidence intervals (as in Section 6.4) and estimated p-values will be presented.

For the alternate primary efficacy endpoint, the comparison of absolute change from baseline to Week 12 in the Pain VAS score will be analyzed using an 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 (as above), and visit by randomized treatment interaction; the model will also include baseline STS use as a fixed effect and baseline Pain VAS score will be included as a covariate. Subject will be fitted as random effect and an unstructured variance-covariance matrix will be used. In case the unstructured variance-covariance results in the lack of convergence, the following covariance structures will be tried in order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, and autoregressive. The difference in least square means (LS Means) with corresponding confidence intervals (as in Section 6.4) and estimated p-values will be presented.

Note, if only one alternate primary is met, a 98% 2-sided CI will also be presented for that alternate primary.

15.1.3. Sensitivity Analysis of Primary Efficacy Variables

15.1.3.1. Sensitivity Analyses with Regard to Missing Primary Endpoint Data

The primary efficacy analyses using the MMRM are performed with the underlying assumption that missing data are MAR. To assess the robustness of the treatment effect under this assumption, sensitivity analyses will be performed in the mITT population under the assumption of MNAR. Pre-specification of a fully exhaustive list of reasons for missing data is difficult to formulate in advance as missing data can arise during trial conduct for a wide variety of reasons not all of which are predictable. However, relatively common reasons for loss of data include, but are not restricted to, dropout due to adverse event, dropout due to lack of efficacy, patient and/or investigator decision to withdraw consent or death.

The first approach for the sensitivity analyses will employ a control-based pattern-mixture model as per Ratitch and O'Kelly (2011) whereby missing observations in both the SN472 and placebo groups are imputed using only data observed in the control group; as such, this approach reflects a 'jump to placebo (reference)' analysis . Mean changes from baseline in BWAT-CUA score will be analyzed based on data observed while the subject remains on study as well as data imputed using multiple imputation (MI) methodology for time points at which no value is observed. Imputation of values in the placebo arm will assume MAR. Imputation of values in the experimental treatment arm will be done as if the subject had been a member of the placebo arm. Imputed values in the experimental treatment arm will be sampled using the imputation model of the placebo arm, i.e., conditional on subject values observed at time points prior to discontinuation relative to the mean of the model for the placebo arm. This approach does not assume a sustained benefit of experimental treatment after discontinuation and limits a post-discontinuation effect to that of placebo and trial effect as reflected in estimated correlations between time points in the placebo arm. The approach will be implemented as follows:

- Step 1: Non-monotone missing data will be imputed first based on the MAR assumption and a multivariate joint Gaussian imputation model using Markov chain Monte Carlo (MCMC) method using the MCMC statement in the SAS® PROC MI procedure. As a result, each imputed dataset will only have missing data at the end of subjects' records, (a monotone missing data pattern). The MCMC method in the MI procedure will be used with multiple chains (option CHAIN=MULTIPLE), 100 burn-in iterations, and a non-informative prior. A separate imputation model will be used for each treatment arm. The imputation models will include the STS use at randomization variable, baseline BWAT-CUA score, and BWAT-CUA scores at each time point. In case of non-convergence or non-estimability issues, a ridge prior and a single model will be considered with treatment arm added as explanatory variable to the model.

- Step 2: The remaining, monotone, missing data for all subjects who discontinue study prematurely will be imputed using sequential regression multiple imputation model estimated based on data from the *placebo arm only*. Each sequential regression model (i.e., for imputation of values at a given time point) will include explanatory variables for the STS use at randomization variable, baseline BWAT-CUA score, and all previous values of BWAT-CUA. Missing values at a given time point in placebo and the experimental treatment arm will be imputed from the same imputation model, conditional on subject values observed or imputed at previous time points. No rounding or range restrictions will be applied to imputed values.
- Step 3: The change from baseline in BWAT-CUA score to each scheduled post-baseline visit will be calculated, based on observed and imputed data. Each of the imputed complete datasets from Step 2 will be analysed with the same MMRM model used for the primary analysis (Section 15.1.2).
- Step 4: The results of the analysis of each imputed dataset, i.e., treatment differences and their standard errors, will be combined using Rubin's imputation rules (Rubin, 1987) to produce pooled estimates of treatment differences, its 95% confidence interval and a pooled p-value. This will be done using SAS® MIANALYZE procedure.

The core SAS code to perform this first sensitivity analysis is contained in Appendix 3.

The second sensitivity analyses will be a tipping point analysis. This will assess the robustness of the alternate primary endpoint analyses by analyzing the penalty to the statistical significance of the primary analysis when adopting a MNAR approach. This will be applied to subjects in the experimental treatment arm with missing data, and a "tipping point" will be identified where statistical significance, being P<0.04 2-sided if both alternate primary endpoints are met or P<0.02 2-sided if only one alternate primary is met, is lost. Note, if neither alternate primary endpoint reaches statistical significance, tipping point analyses will not be applicable. The analyses require that the data has a monotone missingness pattern, thus, if necessary, a partial-imputation method using MCMC will be used. This will be done using the SAS® PROC MI procedure, with sample code given originally above.

The minimum shift parameter will be determined as a small fraction of the estimated treatment effect from the primary analysis; i.e., if the treatment effect estimate from the primary analysis of BWAT-CUA is $\hat{\theta}$, then the minimum shift parameter, δ_{min}, will be set as $\delta_{min} = 0.05 \cdot \hat{\theta}$; and the maximum shift parameter will be set as $\delta_{max} = 40 \cdot \delta_{min} = 2 \cdot \hat{\theta}$, with tipping point analyses executed with no shift parameter (=primary analysis assuming MAR) and between $(\delta_{min}, \delta_{max})$ at intervals of 0.05 creating 40 imputed datasets. Each of these datasets will be analyzed as for the primary analysis using MMRM specified in Section 15.1.2. Results from each tipping point analysis will be combined using Rubin's rule.

The p-values outputted from the models will be displayed along with the treatment effect estimates and associated CIs so that the tipping point for when the significance of the primary analysis is lost can be identified. If the initial shift parameters tested do not identify the tipping

point, the process will be repeated with different shift parameter values (e.g., $\delta_{min} = 0.04 \cdot \hat{\theta}, \ldots., \delta_{min} = 0.01 \cdot \hat{\theta}$) until the tipping point is identified.

The core SAS code perform this analysis is contained in Appendix 4.

The third sensitivity approach will apply a further pattern-mixture analysis using the neighboring-case missing values (NCMV) method as described by Molenberghs and Kenward (2007) to capture different patterns of missingness over time. Imputation of missing data is similar to that described above for the control-based pattern-mixture (jump-to-reference) model. Imputation is made within each pattern of missingness. The analysis then proceeds as per control-based pattern-mixture approach. See the primary analysis Section 15.1.2 for more details and a description of the presentation.

The core SAS code to perform this analysis is contained in Appendix 5.

Similar sensitivity analyses for missing data will be conducted for change from baseline to Week 12 in Pain VAS, score, the other alternate primary endpoint.

15.1.3.2. Sensitivity Analyses with Regard to Missing Baseline Primary Endpoint Data

The primary analyses of BWAT and Pain VAS will be reperformed without the imputation of missing baseline values as described in Section 6.2.

15.1.3.3. Sensitivity Analyses with Regard to Pain Medication Use Over Time

Two supportive sensitivity analyses of the Pain VAS alternate primary endpoint will be made to assess the influence of pain medication use during the trial.

The first approach will be an MMRM model with class terms for STS use, randomized treatment, visit (=week 2, 4, 6, 8, 10 and 12), randomized treatment by visit interaction, pain medication use (measured as morphine milligram equivalent), pain medication by visit interaction, randomized treatment by pain medication interaction and randomized treatment by pain medication by visit interaction; baseline Pain VAS score will be included as a covariate. An unstructured covariance matrix will be used to model the within-subject error. The chief foci of this analysis are (i) the randomized treatment by pain medication interaction term and (ii) the randomized treatment by pain medication by visit interaction term.

The second approach will be a random coefficient MMRM model as described by Hedeker and Gibbons (2006). Class terms will be included for STS and randomized treatment. Visit (week 2, 4, 6, 8, 10 and 12) and pain medication use will be included as continuous variables. The interaction between randomized treatment by pain medication interaction and randomized treatment by pain medication by visit interaction will be the chief foci of this analysis. Inference between randomized treatment will focus on the estimated rate of change of Pain VAS over time on SNF472 vs placebo.

In line with Hedeker and Gibbons (2006), the analysis will be repeated decomposing the within and between subject effects associated with the pain medication time dependent covariate. In this analysis pain medication will be included in the model as (i) mean pain medication use by

subject over time and (ii) within subject mean corrected pain medication use by time. Inference will again focus on the estimated rate of change of Pain VAS over time on SNF472 vs placebo.

The core SAS code for these sensitivity analyses is presented in Appendix 6.

15.2. Secondary Efficacy

The secondary efficacy analyses will be performed hierarchically for the mITT in the order that the parameters appear in the following sub-sections.

15.2.1. Secondary Efficacy Variables, Derivations and Analysis

15.2.1.1. Absolute Change from Baseline to Week 12 in the Wound-QoL Score

The first secondary efficacy endpoint of the absolute change from baseline to Week 12 in Wound-QoL will be analyzed using an MMRM analysis. Wound-QoL (Wound-QoL, 2018) is a questionnaire consisting of 17 items on impairments. Answers to each item are coded with numbers where 0 represents 'not at all' to 4 being 'very much'. A Wound-QoL global score on overall disease-specific quality of life is computed by averaging all items. A global score can only be computed if at least 75% of the items have been answered, i.e., at least 13 in 17 items are valid (Short manual, Wound-QoL, 2018-05-29 [Wound-QoL, 2018]). All the available items' scores will be added up and divided by 17. If there are missing assessments for any one of the 17 items, the median of the scores for a particular item within the associated randomized treatment group will be used for the imputation purposes.

Change from baseline in the Wound-QoL score will be evaluated using an MMRM method similar to the one specified for the primary analysis while substituting BWAT-CUA score related variables in the model with the corresponding Wound-QoL score related variables, such as baseline score and baseline score-by-study visit interaction. See the primary analysis Section 15.1.2 for more details and a description of the presentation.

15.2.1.2. Absolute Change from Baseline to Week 12 in the BWAT Total Score for Primary Lesion

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. BWAT is a standardized quantitative assessment of wound healing that consists of 13 items where each item is rated on a scale of 0 or 1 representing 'best' to 5 representing 'worst'. BWAT total score is the sum of all 13 items with a possible range of scores from 9 to 65. Location and shape items collected in BWAT do not contribute to scoring.

Change from baseline in BWAT total score will be evaluated using an MMRM method similar to the one specified for the primary analysis while substituting BWAT-CUA score related variables in the model with the corresponding BWAT total score related variables, such as baseline score and baseline score-by-study visit interaction. See the primary analysis Section 15.1.2 for more details and a description of the presentation.

15.2.1.3. Qualitative Wound Image Evaluation for the Primary Lesion (Worsened, Equal to, or Improved Relative to Baseline) at Week 12

The wound image evaluation will be collected as part of the non-CRF guideline in qualitative comparison to baseline from Week 12.

The third secondary efficacy endpoint will be analyzed using the generalized estimating equations (GEE) approach. A longitudinal logistic regression model will be fit to the response variable, categorized as an ordinal variable (worsened, equal to or improved). The model will include the predictors: baseline STS use, randomized treatment group, visit (Week 12 Day 5), and visit by randomized treatment interaction. The odds ratio of SNF472 vs placebo along with the associated 95% confidence intervals and p-values will be presented.

The data will be analyzed using the Stuart-Maxwell test which will test the marginal homogeneity for all of the categories (worsened, equal to, or improved) simultaneously.

15.2.1.4. Rate of Change in Opioid Use as Measured in MME from Baseline to Week 12

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 calculation of the pre-specified list of opioids will be based on the formula: strength per unit × (number of units/days supply) × MME conversion factor = MME/day, as specified in the opioid MME conversion guide (CMS, 2017). The maintenance opioid dose will be defined as the average daily opioid dose in MME during the 7-day period 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 using a MMRM model 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 change in use differs between randomized treatments. This is accomplished by using SAS® Proc Mixed statement with the response variable being MME data between Week 1 and Week 12 model fixed variables are treatment, MME baseline value, week and treatment by week interaction and random variables are intercept and week. The treatment effect will be the contrast between SNF472 and placebo slope estimates over 1 to 12 weeks.

The associated slope estimates, difference in slopes, 95% CI, and 2-sided p-value will be extracted from the model and presented.

15.2.2. Missing Data Methods for Secondary Efficacy Variables

As with the primary analysis, sensitivity analyses to explore the influence of missing data will be performed using multiple imputation, tipping-point analyses, and pattern mixture models.

For the secondary endpoints 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 primary lesion and rate of change in opioid use as measured in MME from baseline to Week 12, the control-

based pattern-mixture model as per Ratitch and O'Kelly (2011) as described above for the primary endpoint will be applied. For the ordinal endpoint qualitative wound image evaluation for the primary lesion at Week 12, a similar approach will be employed with monotone logistic regression option in SAS PROC MI.

15.3. Exploratory Efficacy

The exploratory efficacy will be performed on the mITT.

15.3.1. Exploratory Efficacy Variables, Derivations and Analysis

15.3.1.1. Absolute Change from Baseline to Week 12 in Wound Size for the Primary Lesion

The wound size for the primary lesion is collected as a continuous variable of the wound area as measured by imaging software by Tissue Analytics and verified by the reviewing wound expert.

Change from baseline in the wound size will be evaluated using an MMRM method similar to the one specified for the primary analysis while substituting BWAT-CUA score related variables in the model with the corresponding wound size related variables, such as baseline wound size and baseline size-by-study visit interaction. See the primary analysis Section 15.1.2 for more details and a description of the presentation.

15.3.1.2. Absolute Change from Baseline to Week 12 in Each BWAT Item for the Primary Lesion

There are 13 items that comprise BWAT:

- 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 0 or 1 (best) to 5 (worst).

Change from baseline for each individual item will be evaluated using an MMRM method similar to the one specified for the primary analysis (Section 15.1.2).

15.3.1.3. Absolute Change from Baseline in BWAT-CUA, BWAT Total, Pain VAS and Wound-QoL Score by Visit

- BWAT-CUA score is a total of the 8 items of the BWAT assessment, as specified in Section 15.1.1
- BWAT total score is a total of the 13 items of the BWAT assessment, as specified in Section 15.2.1.2
- Pain VAS score is a measurement as specified in Section 15.1.1
- Wound-QoL score is a measurement as specified in Section 15.2.1.1

Change from baseline to each visit (as defined above) for each of these four endpoints will be evaluated using an MMRM method similar to the one specified for the primary analysis while substituting BWAT-CUA score related variables in the model with the corresponding (BWAT Total, Pain VAS and Wound-QoL) score-related variables for the other endpoints, such as baseline score and baseline score-by-study visit interaction. The model will be restricted to baseline and the visit of interest as well as the intermediary visits. The least squares mean of the treatment difference at the visit of interest will be reported with the difference, confidence interval, and p-value included. See the primary analysis Section 15.1.2 for more details and a description of the presentation.

15.3.1.4. Proportion of Subjects with the New CUA Lesions Between Baseline and Week 12

The new CUA lesion will be collected in the New CUA Lesion (Wound) CRF page.

The proportion of subjects with the new CUA lesions since baseline will be considered as a binary response (no new lesions vs 1 or more new lesions). The model will use exact logistic regression with stratification for STS use at baseline and include randomized treatment group, time of the lesion assessment (Week 6 or Week 12) and time-by-treatment interaction. The odds ratio estimate for SNF472: placebo at each time point (and overall at any time point) will be presented along with the associated confidence interval.

15.3.1.5. Absolute change from baseline to Week 12 in the Wound-QoL scores for the body, everyday life, and psyche

The Wound-QoL subscale scores will be evaluated using an MMRM similar to that described for the Wound-QoL global score in Section 15.2.1.1. There are three subscales of Wound-QoL score: ‘body’, ‘psyche’ and ‘everyday life’. For subscale ‘Body’, items #1 through #5 are averaged out. For subscale ‘Psyche’, items #6 to #10 are averaged out. For subscale ‘Everyday life’, items #11 to #16 are averaged out (Note: Item #17 is not part of any of the subscales). A subscale can only be computed if no more than 1 item of the subscale is missing. For example, if for subscale ‘Body’, one item is missing, the average is going to be all of the remaining items’ scores added up and divided by 4. If there are missing assessments for any one items within a subscale, the median of the scores for a particular item within the associated randomized treatment group will be used for the imputation purposes. Descriptive statistical summaries will be generated for individual questions as well.

15.3.1.6. Absolute Change from Baseline to Week 12 in the BWAT-CUA Score for the Secondary and Tertiary Lesions

The BWAT-CUA score will be evaluated as specified in Section 15.1.1 for each of the secondary and tertiary lesions.

Change from baseline in the BWAT-CUA score of the secondary and tertiary lesions will be evaluated using an MMRM method similar to the one specified for the primary analysis while substituting BWAT-CUA score of the primary lesion related variables in the model with the corresponding BWAT-CUA score for secondary and tertiary related variables, such as baseline score and baseline score-by-study visit interaction. See the primary analysis Section 15.1.2 for more details and a description of the presentation.

15.3.1.7. Proportion of Subjects Requiring an Increase in Pain Medication Related to their CUA lesion(s) Between Baseline and Week 12

CUA wound pain medication will be recorded on the CUA pain medication CRF.

The proportion of subjects with an increase in pain medication will be considered as a binary response (pain medication increased since baseline vs pain medications decreased or stayed the same compared with baseline). The model applied and results presented will be the same as that described for new CUA lesions above (Section 15.3.1.4).

15.3.1.8. Proportion of Subjects with a Decrease in Pain Medication Related to their CUA Lesion(s) Between Baseline and Week 12

The proportion of subjects with a decrease in pain medication will be considered as a binary response (pain medication decreased since baseline vs pain medications increased or stayed the same compared with baseline).

15.3.1.9. Absolute Change from Baseline to Week 12 in Opioid Use as Measured in MME

Opioid use as measured in MME will be used as specified in Section 15.2.1.4.

Change from baseline in the opioid use will be evaluated using an MMRM method similar to the one specified for the primary analysis while substituting BWAT-CUA score related variables in the model with the corresponding opioid use related variables, such as baseline score and baseline score-by-study visit interaction. See the primary analysis Section 15.1.2 for more details and a description of the presentation.

15.3.1.10. Absolute Change from Baseline to Week 24 vs Week 12 in the BWAT-CUA Score for the Primary Lesion

The absolute change from baseline to Week 24 vs Week 12 is the change from baseline at Week 24 minus change from baseline at Week 12.

BWAT-CUA score is a total of the 8 items of the BWAT assessment, as specified in Section 15.1.1.

The paired t-test will be used to test the mean difference between the two sets of observations for the subjects in Part 2 between Week 24 and Week 12 for the BWAT-CUA score for the primary lesion. The mean of the differences, standard deviation, corresponding 95% confidence intervals and p-value will be presented.

15.3.1.11. Absolute Change from Baseline to Week 24 vs Week 12 in the Pain VAS Score

Pain VAS score is a measurement as specified in Section 15.1.1.

Change from baseline in the VAS scores will be evaluated using a paired t-test method similar to the one specified in Section 15.3.1.10 while substituting BWAT-CUA score for the primary lesion related variables with the corresponding Pain VAS score related variables.

15.3.1.12. Absolute Change from Baseline to Week 24 vs Week 12 in the Wound-QoL Score

Wound-QoL score is a measurement as specified in Section 15.2.1.1.

Change from baseline in the Wound-QoL scores will be evaluated using a paired t-test method similar to the one specified in Section 15.3.1.10 while substituting BWAT-CUA score for the primary lesion related variables with the corresponding Wound-QoL score related variables.

15.3.1.13. Absolute Change from Baseline to Week 24 vs Week 12 in the BWAT Total Score for the Primary Lesion

BWAT total score is a total of the 13 items of the BWAT assessment, as specified in Section 15.2.1.2.

Change from baseline in the BWAT total scores will be evaluated using a paired t-test method similar to the one specified in Section 15.3.1.10 while substituting BWAT-CUA score for the primary lesion related variables with the corresponding BWAT total score related variables.

15.3.1.14. Qualitative Wound Image Evaluation for the Primary Lesion at Week 24 vs Week 12 (Worsened, Equal to, or Improved Relative to Baseline) for the Primary Lesion

Qualitative wound image evaluation for the primary lesion (worsened, equal to, or improved relative to baseline) is measured as specified in Section 15.2.1.3.

The data will be analyzed using the Stuart-Maxwell test which will test the marginal homogeneity for all of the categories (worsened, equal to, or improved) simultaneously.

15.3.1.15. Absolute Change from Baseline to Week 24 vs Week 12 in Wound Size for the Primary Lesion

The wound size for the primary lesion is collected as a continuous variable of the wound area as measured by imaging software by Tissue Analytics and verified by the wound expert review.

Change from baseline in the wound size for primary lesion will be evaluated using a paired t-test method similar to the one specified in Section 15.3.1.10 while substituting BWAT-CUA score for the primary lesion related variables with the corresponding wound size related variables.

15.3.1.16. Absolute Change from Baseline to Week 24 vs Week 12 of each BWAT Item for the Primary Lesion

Each BWAT assessment contains 13 items as specified in Section 15.3.1.2 .

Change from baseline in each BWAT individual item score will be evaluated using a paired t-test method similar to the one specified in Section 15.3.1.10 while substituting BWAT-CUA score for the primary lesion related variables with the corresponding BWAT individual item score related variables.

15.3.1.17. Absolute Change from Week 24 to the Follow-up Visit in the BWAT-CUA Score for Primary Lesion

Absolute change from baseline to Week 24 to the follow up visit is defined as change from baseline at follow-up visit value minus change from baseline at Week 24 visit value.

BWAT-CUA score is a total of the 8 items of the BWAT assessment, as specified in Section 15.1.1.

The paired t-test will be used to test the mean difference between the two sets of observations for the subjects in Part 2 between the follow-up visit and Week 12 for the BWAT-CUA score for the primary lesion. The mean of the differences, standard deviation, corresponding 95% confidence intervals and p-value will be presented.

15.3.1.18. Absolute Change from Week 24 to the Follow-up Visit in the Pain VAS Score

Pain VAS score is a measurement as specified in Section 15.1.1.

Change from baseline in the Pain VAS scores will be evaluated using a paired t-test method similar to the one specified in Section 15.3.1.17 while substituting BWAT-CUA score for the primary lesion related variables with the corresponding Pain VAS score related variables.

15.3.2. Missing Data Methods for Exploratory Efficacy Variables

There will be no multiple imputation or tipping point analysis for the exploratory endpoints.

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the safety population.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section for Part 1. For Part 2, subjects who were on Placebo and subjects who were on SNF472 in Part 1 will be presented separately in Part 2.

16.1. Adverse Events

Adverse Events (AEs) will be coded using MedDRA version 23.1 or later.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study drug. Part 1 TEAEs are those that started on or after

first dose in part 1 but before 1st dose in part 2. Part 2 TEAEs are those that started on or after 1st dose in part 2, up to and including on the last day of dose in part 2. AEs that started after the last day of dose, but within 30 days of last dose will be considered as emergent during follow-up. If patients do not proceed to part 2, then TEAEs will be defined for part 1 and follow-up only, using the same approach.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e., treatment emergent.

An overall summary of number of subjects within each of the categories described in the sub-section below, will be provided as specified in the templates.

Listings will include TEAEs and Non-TEAEs.

16.1.1. All TEAEs

Incidence of TEAEs will be presented by treatment group, study period (Part 1, Part 2 and follow-up period of 30 days), System Organ Class (SOC) and Preferred Term (PT) and broken down further by maximum severity and relationship to study drug.

16.1.1.1. Severity and Intensity

The intensity is classified according to the Common Terminology Criteria for Adverse Events (CTCAE): Grade 1 is Mild, Grade 2 is Moderate, Grade 3 is Severe, Grade 4 is Life-threatening, and Grade 5 is Fatal. TEAEs with a missing severity will be classified as severe. If a subject reports a TEAE more than once within that SOC/ PT, the AE with the worst case severity/intensity will be used in the corresponding severity summaries.

16.1.1.2. Relationship to Study Drug

Relationship, as indicated by the Investigator, is classed as “related” and “not related”. TEAEs with a missing relationship to study drug will be regarded as “related” to study drug.

16.1.2. TEAEs Leading to Discontinuation of Study drug

TEAEs leading to permanent discontinuation of study drug will be identified by using the question “Action Taken with study drug” on the CRF AE page.

Adverse events will continue to be collected for 30 days after last dose of study drug 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.

For TEAEs leading to discontinuation of study drug, summaries of incidence rates (frequencies and percentages) by treatment group, study period (Part 1, Part 2 and follow-up), SOC and PT will be prepared.

16.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as “Serious” on the Adverse Events page of the (e)CRF. A summary of serious TEAEs by treatment group, study period (Part 1, Part 2 and follow-up), SOC and PT will be prepared.

16.1.4. Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded as “Fatal” on the Adverse Events page of the (e)CRF. A summary of TEAEs leading to death by treatment group, study period (Part 1, Part 2 and follow-up), SOC and PT will be prepared.

16.1.5. CUA Wound-Related Adverse Events

The CUA wound-related AEs will be presented based on the “Is this a CUA wound-related complication?” question from the Adverse Events eCRF page. A summary of CUA wound-related complications will be presented by the treatment group, SOC and PT for Part 1, and by SOC and PT for Part 2 and follow-up will be prepared.

16.1.6. Treatment-Related Adverse Events

Treatment-related AEs are the treatment-emergent AEs which have a “related” relationship to the study drug. A summary of treatment-related AEs by study period (Part 1, Part 2 and follow-up), SOC and PT will be prepared.

16.2. Deaths

If any subjects die during the study, as recorded on the “Death Details” page of the (e)CRF, the information will be presented in a summary table and a data listing.

16.3. Hemodialysis-Related Events

HD-related events collected in the CRF page “Hemodialysis Related Events” will be summarized using counts and percentages by treatment group and study period (Part 1, Part 2 and follow-up).

16.4. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for hematology, chemistry (including ionized calcium, parathyroid hormone (PTH), high-sensitivity C-reactive protein (hs-CRP)), and serum pregnancy test for females of childbearing potential. A list of laboratory assessments to be included in the outputs is included in Table 4 of the protocol.

Presentations will use SI Units.

Quantitative laboratory measurements reported as “< X”, i.e., below the lower limit of quantification (BLQ), or “> X”, i.e., above the upper limit of quantification (ULQ), will be

converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e., as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements) by panel (hematology or chemistry), test, timepoint for Part 1, Part 2, Follow up as well as from Week 12 to Week 24 by panel and test.
- Incidence of abnormal values according to normal range criteria by panel, test, treatment group and at any timepoint post-baseline but within 30 days after the last dose.
- Individual patient changes in chemistry and hematology parameters will be shown with scatter plots comparing baseline value and post-baseline value for each post-baseline timepoint. A 45-degree line and the upper and lower limits of normal will be displayed for reference.
- Listing of subjects meeting abnormal criteria by panel, test, treatment group and time point.

16.4.1. Laboratory Reference Ranges and Abnormal Criteria

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as collected:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

16.5. Holter Monitoring and Electrocardiograms

Holter data will be analyzed centrally by extracting triplicate ECGs from the records at each of the following timepoints: pre-dose, end of infusion (EOI), and end of dialysis. 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 baseline will be the last non-missing record of Holter monitoring prior to the first dose of the study drug. The mean of the three results will be used for the presentation purposes.

Results from the centrally analyzed extracted ECGs will be included in the reporting of this study.

The following ECG parameters will be reported for this study:

- PR Interval (msec)
- QRS Interval (msec)
- RR Interval (msec)
- QT Interval (msec)

- QTcF Interval (msec) [derived]
- QTcB Interval (msec) [derived]
- HR (bpm)

The following summaries will be provided for the Holter-extracted ECG data:

- Counts and percentages by treatment group for Part 1 at any timepoint post-baseline and counts and percentages for Part 2 subjects by randomized group at any timepoint post-baseline
- Actual and change from baseline by visit (for quantitative measurements)
- Listing of subjects meeting abnormal criteria

16.5.1. ECG Specific Derivations

- Bazett's Correction (msec)

$$QTcB\ (\text{msec}) = \frac{QT\ (ms)}{\sqrt{RR\ (ms)/1000}}$$

- Fridericia's Correction (msec)

$$QTcF\ (\text{msec}) = \frac{QT\ (ms)}{\sqrt[3]{RR\ (ms)/1000}}$$

- RR Interval – If RR Interval is not available it will be derived from HR as follows, for the derivation of the QTc corrections

$$RR\ (\text{msec}) = 1000 * \frac{60}{HR\ (bpm)}$$

All the components for the calculations need to be collected at the same assessment. If one or more is missing, then then the value will not be calculated.

16.5.2. ECG Markedly Abnormal Criteria

Markedly abnormal quantitative ECG measurements (mean of the triplicate extracted ECG results from the central reading) will be summarized in accordance with the following predefined markedly abnormal criteria:

- For baseline, each timepoint, and any post-baseline ECG in Part 1 and Part 2, absolute values for QT interval, QTcB interval and QTcF will be classified as:
  - ≤ 450 msec
  - > 450 msec
  - > 480 msec

  - > 500 msec

- Change from Baseline to each timepoint and any post-baseline ECG in Part 1 and Part 2, for QT interval, QTcB interval and QTcF will be classified as:
  - >30 msec increase from baseline
  - >60 msec increase from baseline

Note: The ranges are not mutually exclusive. For example, if a subject has a value of more than 500 msec, they will be counted in the >450, > 480, and >500 category.

16.5.3. Holter Arrhythmia Analysis

Holter reading will be performed centrally and parameters related to the following will be reported and summarized:

- Rhythm profile
- Arrhythmias, rate and RR interval trends
- Holter events or findings

16.6. Vital Signs

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (°C)
- Post-dialysis Weight (kg)

The following summaries, will be provided for vital signs data:

- Actual and change from baseline by treatment group and timepoint

16.7. CUA Wound Care

Wound care received for CUA lesions, as collected on the CRF page “Lesion (Wound) Care”, will be listed by subject and summarized by treatment group

16.8. Physical Examination

Physical examination findings will be listed by subject.

17. DIALYSIS PARAMETERS

Dialysis parameters include:

- Calcium concentration in the dialysate
- Dialysis frequency
- Dialysis duration
- Clearance time / volume (Kt/V)
- Urea reduction ratio (URR) (%)

The dialysis parameters will be summarized by a parameter, treatment group and visit.

18. REFERENCES

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APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IDDI OUTPUT CONVENTIONS

Outputs will be presented according to the following:

1. ABBREVIATIONS

ASCII American standard code for information interchange file format

CGM Computer graphics metafile

ODS Output Delivery System

RTF Rich text file format

2. INTRODUCTION

This document applies to standards used for outputting tables, listings and figures. It is intended to provide specifications to guide the statistician or statistical programmer in setting up specifications for programming tables, listings and figures. These standards should be used in the absence of customer specific standards.

3. OUTPUT FILE NAMING CONVENTIONS

As far as possible, output files should be in RTF format, although .DOC files are also permitted.

The program, program log and output file name should reflect the type and number of the statistical output. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('t' for table, 'l' for listing and 'f' for figure). If there is only 1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (e.g., t14_3_01_1.rtf)

4. PAPER SIZE, ORIENTATION AND MARGINS

The size of paper will be Letter for the United States, otherwise A4.

The page orientation should preferably be landscape, but portrait is also permitted.

5. TABLE AND LISTING OUTPUT CONVENTIONS

Univariate Statistics:

- Statistics should be presented in the same order across tables

- Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
  - Minimum and maximum: N
  - Mean, median and CV%: N + 1
  - SD: N + 2

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:
  - 77 (100.0%)
  - 50 (64.9%)
  - 0 (0.0%)
- Percentages will be reported to one decimal place, except percents <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percents < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.
  - <0.1%
  - 6.8%
  - >99.9%

  Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
- Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:

- An example is given below:
  - (-0.12, -0.10)
  - (9.54, 12.91)

P-values:

- P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule.

6. EXAMPLE

Customer Name - Protocol Number

Table 14.1.1.1
Subject Disposition

	Number (%) of Subjects		
	Treatment		
Disposition	A (N=XX)	B (N=XX)	Total (N=XX)
Randomized	XX	XX	XX
Completed	XX (XXX.X%)	XX (XXX.X%)	XX (XXX.X%)
Discontinued	XX (XXX.X%)	XX (XXX.X%)	XX (XXX.X%)
Reasons for Discontinuation:			
XXXXXXXXXXXX	XX (XXX.X%)	XX (XXX.X%)	XX (XXX.X%)
XXXXXXXXXXXX	XX (XXX.X%)	XX (XXX.X%)	XX (XXX.X%)

SOURCE: Listing 16.2.1.1 Page 1 of 1
Abbreviations / definitions
Formulae
P-values...
Symbols...
NOTE 1: Treatment A=XXXXXXXXXXXXXXXXXX.
B=XXXXXXXXXXXXXXXXXX.
NOTE 2: ...

X:\CUSTOMER\COMPOUND\STUDY\BIOSTATISTICS\PRODUCTION\TABLES\T14_1_1_1.SAS
DDMMMYYYY HH:MM

7. DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-dd and hh:mm:ss.

8. SPELLING FORMAT

English US

9. PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	**For Tables and Graphs**
SNF472	SNF472
Placebo	Placebo
Not Randomized	Not Randomized
Not Treated	Not Treated

10. PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	**Short Name**
Screening Visit 1	Scr1
Screening Visit 2	Scr2
Baseline Week 1 Day 1	BL
Week 1 Day 3	W1D1
Week 1 Day 5	W1D3
Week 2 Day 1	W2D1
Week 2 Day 3	W2D3
Week 2 Day 5	W2D5
Week 3 Day 1	W3D1
Week 3 Day 3	W3D3
Week 3 Day 5	W3D5
Week 4 Day 1	W4D1
Week 4 Day 3	W4D3
Week 4 Day 5	W4D5
Week 5 Day 1	W5D1
Week 5 Day 3	W5D3
Week 5 Day 5	W5D5
Week 6 Day 1	W6D1
Week 6 Day 3	W6D3
Week 6 Day 5	W6D5
Week 7 Day 1	W7D1
Week 7 Day 3	W7D3
Week 7 Day 5	W7D5
Week 8 Day 1	W8D1

Long Name (default)	Short Name
Week 8 Day 3	W8D3
Week 8 Day 5	W8D5
Week 9 Day 1	W9D1
Week 9 Day 3	W9D3
Week 9 Day 5	W9D5
Week 10 Day	W10D1
Week 10 Day 3	W10D3
Week 10 Day 5	W10D5
Week 11 Day 1	W11D1
Week 11 Day 3	W11D3
Week 11 Day 5	W11D5
Week 12 Day 1	W12D1
Week 12 Day 3	W12D3
Week 12 Day 5	W12D5
Week 13 Day 1	W13D1
Week 13 Day 3	W13D3
Week 13 Day 5	W13D5
Week 14 Day 1	W14D1
Week 14 Day 3	W14D3
Week 14 Day 5	W14D5
Week 15 Day 1	W15D1
Week 15 Day 3	W15D3
Week 15 Day 5	W15D5
Week 16 Day 1	W16D1

Long Name (default)	Short Name
Week 16 Day 3	W16D3
Week 16 Day 5	W16D5
Week 17 Day 1	W17D1
Week 17 Day 3	W17D3
Week 17 Day 5	W17D5
Week 18 Day 1	W18D1
Week 18 Day 3	W18D3
Week 18 Day 5	W18D5
Week 19 Day 1	W19D1
Week 19 Day 3	W19D3
Week 19 Day 5	W19D5
Week 20 Day 1	W20D1
Week 20 Day 3	W20D3
Week 20 Day 5	W20D5
Week 21 Day 1	W21D1
Week 21 Day 3	W21D3
Week 21 Day 5	W21D5
Week 22 Day 1	W22D1
Week 22 Day 3	W22D3
Week 22 Day 5	W22D5
Week 23 Day 1	W23D1
Week 23 Day 3	W23D3
Week 23 Day 5	W23D5
Week 24 Day 1	W24D1

Long Name (default)	**Short Name**
Week 24 Day 3	W24D3
Week 24 Day 5/Early Termination	W24D5/ET
Follow up	FU

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study drug start date, then not TEAE If start date >= study drug start date, then TEAE
	Partial	If start date < study drug start date, then not TEAE If start date >= study drug start date, then TEAE
	Missing	If start date < study drug start date, then not TEAE If start date >= study drug start date, then TEAE
Partial, but known components show that it cannot be on or after study drug start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then:

START DATE	STOP DATE	ACTION
		If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE

Note: if an AE starts on the same day as first dose of study drug, the time of onset of the AE (if known) will be taken into account when determining treatment emergence.

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date assign as concomitant
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date assign as concomitant

START DATE	STOP DATE	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant
Missing	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Missing	Assign as concomitant

APPENDIX 3. A CONTROL-BASED PATTERN-MIXTURE MODEL SENSITIVITY ANALYSIS

A control-based pattern-mixture model approach as per Ratitch and O'Kelly (2011) whereby missing observations in both the SN472 and placebo groups are imputed using only data observed in the control group; this model reflects a 'jump to placebo (reference)' analysis.

Several steps are required to execute this sensitivity analysis.

In the first step, intermittently missing data (e.g., where a subject has week 2 and week 6 data recorded but has week 4 data missing) are imputed as non-monotone missing to generate a monotone missing pattern. The form of the associated SAS code is given below where the dataset **DATAIN** has already been sorted by randomized treatment (**RANDTRT**) and the stratification variable of intravenous **STS** use at of randomization:

```
/*FIRST STEP IMPUTE NON-MONOTONE(INTERMITTENTLY)MISSING DATA*/
PROC MI DATA=DATAIN SEED=<VALUE> NIMPUTE=20 OUT=MI_OUT1;
 VAR BASE W2 W4 W6 W8 W10 W12;
   MCMC CHAIN=MULTIPLE PRIOR=JEFFREYS IMPUTE=MONOTONE;
   BY RANDTRT STS;
RUN;
```

where **BASE** = baseline BWAT-CUA score, and **W2, W4, …,W12 =** week 2, 4, …12 post baseline BWAT-CUA scores.

The resulting dataset **MI_OUT1** is then sorted by **_IMPUTATION_** , **RANDTRT** and **STS**. In the second step, **PROC MI** is called again utilizing the regression method under **MNAR** to complete imputation of the monotone missing datasets resulting from the first step. The SAS code will be of the following form:

```
/*SECONDLY IMPUTE MONOTONE MISSING DATA AS MNAR JUMP TO PLACEBO*/
   PROC MI DATA=MI_OUT1 SEED = <SEED> NIMPUTE = 1 OUT=MI_OUT2;
      BY_IMPUTATION_;
      CLASS RANDTRT STS;
      MONOTONE REG (W2 W4 W6 W8 W10 W12 = BASE STS / DETAILS);
      MNAR MODEL (W2 W4 W6 W8 W10 W12 / MODELOBS =(RANDTRT = 'PLACEBO'));
      VAR W2 W4 W6 W8 W10 W12 BASE STS;
RUN;
```

The dataset **MI_OUT2** contains the 20 complete imputed data sets. This dataset will be transformed in a third step such that, for each subject, each post-baseline time-point is represented by a separate record.

```
/*THIRD STEP TRANSFORM IMPUTED DATASETS*/
DATA MI_OUT3; SET MI_OUT2;
  VISIT=2; BWATCUA_CHG_BL=W2-BASE; OUTPUT;
  VISIT=4; BWATCUA_CHG_BL=W4-BASE; OUTPUT;
```

```
  VISIT=6; BWATCUA_CHG_BL=W6-BASE; OUTPUT;
  VISIT=8; BWATCUA_CHG_BL=W8-BASE; OUTPUT;
  VISIT=10; BWATCUA_CHG_BL=W10-BASE; OUTPUT;
  VISIT=12; BWATCUA_CHG_BL=W12-BASE; OUTPUT;
RUN;
```

The 20 complete datasets in **MI_OUT3** will then be analyzed in a fourth step by MMRM via **PROC MIXED** as specified for the primary endpoint. The SAS code will be of the following form:

```
/*FOURTH STEP MMRM ANALYSIS OF IMPUTED DATASETS*/
PROC MIXED DATA=MI_OUT3 METHOD=REML;
   BY _IMPUTATION_;
   CLASS PATIENT RANDTRT VISIT STS;
   MODEL BWATCUA_CHG_BL = BASE RANDTRT VISIT RANDTRT*VISIT STS /DDFM=KR;
   REPEATED VISIT / PATIENT = PATIENT TYPE = UN;
   LSMEANS RANDTRT*VISIT/SLICE=VISIT PDIFF DIFF ALPHA=0.04 CL;
   ODS OUTPUT DIFFS=DIFF LSMEANS=LSMEANS;
RUN;
```

To obtain overall LSmean and treatment effect estimates, the **DIFF** and **LSMEANS** datasets are merged in a fifth step prior to combination across imputations using Rubin's rule in a sixth step via **PROC MIANALYZE**. The SAS code will be of the following form:

```
/*FIFTH STEP MERGE DIFF AND LSMEANS DATASETS*/
DATA DIFF2;
   SET DIFF (IN=A) LSMEANS;
   IF A THEN COMPARISON=RANDTRT||' VS '||LEFT(_RANDTRT);
   ELSE COMPARISON=RANDTRT;
RUN;

PROC SORT DATA=DIFF2;
   BY COMPARISON _IMPUTATION_;
RUN;

/*SIXTH STEP COMBINE MI ESTIMATES VIA MERGE DIFF AND LSMEANS DATASETS*/
PROC MIANALYZE DATA=DIFF2;
   BY COMPARISON;
   MODELEFFECTS ESTIMATE;
   STDERR STDERR;
ODS OUTPUT PARAMETERESTIMATES=MIESTS;
RUN;
```

The output dataset **MIESTS** contains the final, imputed results. The resulting multiply imputed means and difference in means between SNF472 and placebo will be presented, along with the associated SEs, CIs and 2-sided p-values.

Exactly the same approach will be used for the analysis of the alternate primary endpoint, Pain VAS score.

APPENDIX 4. TIPPING POINT SENSITIVITY ANALYSIS

A tipping point analysis whereby missing data are imputed in the SNF472 arm with an increasing degree of penalization and thus find the 'tipping point', i.e., that degree of penalization that renders a positive p-value for the principal analyses of the primary endpoint non-significant.

All imputation steps are as described in Appendix 3 for the control-based pattern-mixture model above, apart from the second step where monotone missing data are imputed for patients randomized to SNF472 are adjusted using the **ADJUST** and **SHIFT** options:

```
/*SECONDLY APPYING TIPPING POINT IMPUTATION*/
   PROC MI DATA=MI_OUT1 SEED = <SEED> NIMPUTE = 1 OUT=MI_OUT2<DELTA>;
      BY_IMPUTATION_;
      CLASS RANDTRT STS;
      MONOTONE REG (W2 W4 W6 W8 W10 W12 = BASE <COVS> STS / DETAILS);
      MNAR ADJUST (W2 W4 W6 W8 W10 W12 / SHIFT = <DELTA> ADJUSTOBS =(RANDTRT =
      'PLACEBO'));
      VAR W2 W4 W6 W8 W10 W12 BASE <COVS> STS;
RUN;
```

The value of **<DELTA>** is progressively increased and the code re-run for each increase. This generates a series of **MI_OUT2<DELTA>** datasets. To each of these datasets, steps 3 to 6 as described for the control-based pattern-mixture model will be applied, thus giving rise to a multiply imputed treatment effect estimate for each value of **<DELTA>** for SNF472 vs placebo, along with its SE and CI. These treatment effect estimates and CIs will be plotted in a stacked forest plot format vs **<DELTA>**. The first value of **<DELTA>** whereby the CI includes zero will be identified as the tipping point.

APPENDIX 5. PATTERN MIXTURE NEIGHBORING-CASE SENSITIVITY ANALYSIS

A second pattern-mixture analysis using the neighboring-case missing values (NCMV) method as described by Molenberghs and Kenward (2007). All imputation steps are as described in Appendix 3 apart from the second step where monotone missing data are imputed using the **MNAR (MODELOBS=NCMV)** option:

```
/*SECONDLY IMPUTE MONOTONE MISSING DATA VIA PATTERN-MIXTURE APPROACH WITH
  NEIGHBOURING-CASE MISSING VALUES APPROACH*/
    PROC MI DATA=MI_OUT1 SEED = <SEED> NIMPUTE = 1 OUT=MI_OUT2;
      BY _IMPUTATION_ RANDTRT STS;
        MONOTONE REG (W2 W4 W6 W8 W10 W12 = BASE <COVS> / DETAILS);
        MNAR MODEL (W2 W4 W6 W8 W10 W12 / MODELOBS =NCMV);
        VAR W2 W4 W6 W8 W10 W12 BASE <COVS>;
RUN;
```

APPENDIX 6. SENSITIVITY ANALYSES REGARDING PAIN MEDICATION USE

Two supportive sensitivity analyses of the Pain VAS alternate primary endpoint. The first approach will be an MMRM model with class terms for STS use, randomized treatment, visit (=week 2, 4, 6, 8, 10 and 12), randomized treatment by visit interaction, pain medication use (measured as morphine milligram equivalent), pain medication by visit interaction, randomized treatment by pain medication interaction and randomized treatment by pain medication by visit interaction; baseline Pain VAS score will be included as a covariate. An unstructured covariance matrix will be used to model the within-subject error.

The chief foci of this analysis are (i) the randomized treatment by pain medication interaction term and (ii) the randomized treatment by pain medication by visit interaction term.

The core SAS code will be of the form:

```
PROC MIXED DATA=DATAIN;
   CLASS PATIENT RANDTRT VISIT STS PAIN;
   MODEL   VAS_CHG_BL = BASE RANDTRT VISIT PAIN RANDTRT*VISIT
           VISIT*PAIN RANDTRT*PAIN RANDTRT*VISIT*PAIN;
   REPEATED VISIT / SUBJECT = PATIENT(RANDTRT) TYPE=UN;
   LSMEANS RANDTRT*PAIN/PDIFF DIFF ALPHA=0.04 CL;
   LSMEANS RANDTRT*VISIT*PAIN/SLICE=VISIT*PAIN PDIFF DIFF ALPHA=0.04 CL;
   ODS OUTPUT DIFFS=DIFF LSMEANS=LSMEANS;
RUN;
```

The second approach will be a random coefficient MMRM model as described by Hedeker and Gibbons (2006). Class terms will be included for STS and randomized treatment. Visit (=week 0, 2, 4, 6, 8, 10 and 12) and pain medication use will be included as continuous variables. The interaction between randomized treatment by pain medication interaction and randomized treatment by pain medication by visit interaction will be the chief foci of this analysis. Inference between randomized treatment will focus on the estimated rate of change of Pain VAS over time on SNF472 vs placebo.

The core SAS code will be of the form:

```
DATA DATAIN;
  RANDTRT_VISIT = RANDTRT*VISIT;
RUN;

PROC MIXED DATA = DATAIN;
 CLASS PATIENT;
 MODEL VAS_CHG_BL = STS RANDTRT VISIT RANDTRT_VISIT PAIN /SOLUTION;
 RANDOM INTERCEPT VISIT /SUB=PATIENT(RANDTRT) TYPE=UN G GCORR;
RUN;
```

In line with Hedeker and Gibbons (2006), a further analysis will be performed to decompose the within and between subject effects associated with the pain medication time dependent covariate. In this analysis pain medication will be included in the model as (i) mean pain

medication use by subject over time and (ii) within subject mean corrected pain medication use by time. Inference will again focus on the estimated rate of change of Pain VAS over time on SNF472 vs placebo.

The core SAS code will be of the form:

```
PROC SORT DATA = DATAIN;
    BY PATIENT VISIT;
RUN;

PROC MEANS DATA = DATAIN NOPRINT;
    CLASS PATIENT;
    VAR PAIN;
    OUTPUT OUT = MEANPAIN_BY_PATIENT MEAN = MPAIN;
RUN;

DATA DATAIN;
    MERGE DATATIN MEANPAIN_BY_PATIENT;
    BY PATIENT;
    PAINI = PAIN – MPAIN;
RUN;

PROC MIXED DATA = DATAIN METHOD=ML COVTEST;
  CLASS PATIENT;
  MODEL VAS_CHG_BL = STS RANDTRT VISIT RANDTRT_VISIT MPAIN PAINI /SOLUTION;
  RANDOM INTERCEPT VISIT /SUB=PATIENT(RANDTRT) TYPE=UN G GCORR;
RUN;
```

CALCIPHYX

Title	**Addendum to Statistical Analysis Plan (Version 1.3)**
Date	10 APR 2023
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	SNFCT2017-06
Sponsor	Sanifit Therapeutics SA

Approvals

Name and Role	Signature and Date
[redacted] Sanifit Therapeutics SA	[redacted]
[redacted] KJC Statistics Ltd	[redacted]
[redacted] International Drug Development Institute	[redacted]

ADDENDUM TO STATISTICAL ANALYSIS PLAN VERSION 1.3- SUMMARY OF CHANGES FROM VERSION 1.2

There have been no updates to the Addendum.

ADDENDUM TO STATISTICAL ANALYSIS PLAN

If due to operational issues, the sample size re-estimation (SSRE) takes place with >50% (33/66) of subjects, the Cui, Hung and Wang fixed weight methodology for the SSRE and primary endpoint analysis will remain the same. For example, if the SSRE takes place with p% (>50%) of subjects, the combination of patient data pre and post the SSRE will use weights of $\sqrt{p}$ and $\sqrt{1-p}$, respectively. Regardless of the fraction of subjects included in the SSRE, the pre-specified minimum and maximum final sample size of 66 and 99 subjects, respectively, will not change.