Clinical Trial Protocol Incorporating Amendment 1, 2, and 3

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

Sponsor:
Laboratoris Sanifit
Europa Building, 2nd floor
07121 Palma de Mallorca
SPAIN

Academic Research Organisation:
[redacted]

Principal Investigator:
[redacted]

ARO Protocol No: 15-091
Sponsor Protocol No: SNFCT2015_04

EudraCT: 2015-004313-25

Investigational Medicinal Product Name: SNF472

Development Phase: Phase 2a
Date of Protocol: V4 dated 11 April 2017

Protocol/Amendment	Date	Type of Amendment
Protocol Final	02 December 2015	Not applicable
Amendment 1	10 March 2016	Substantial
Amendment 1.1		Right to Amend Request from MHRA
Amendment 2	08 October 2016	Substantial
Amendment 3	11 April 2017	Substantial

This Clinical Trial will be conducted according to the clinical trial protocol and in compliance with Good Clinical Practice, with the Declaration of Helsinki (Version 1996) and with other applicable regulatory requirements.

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SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Expert

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

This Clinical Trial Protocol was subjected to critical review and has been released by the Sponsor. The information that it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (1996), and the guidelines on Good Clinical Practice applicable to this clinical trial. This clinical trial involves research.

Sponsor Signatory/Responsible Medical Expert

[redacted] Date

Medical Monitor

Laboratoris Sanifit.

[redacted] Date

Chief Scientific Officer
Laboratoris Sanifit.

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SIGNATURE PAGE

Declaration of the Principal Investigator

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Principal Investigator

[redacted]

Date

Principal Investigator
[redacted]

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PROTOCOL SYNOPSIS

Protocol Title:	*Phase 2 Open Label Single Arm Repeat Dose Study to Assess the Effect of SNF472 on Wound Healing in Uraemic Calciphylaxis Patients*
Study Numbers:	15-091 (CTC-A)
Sponsor Protocol No.:	SNFCT2015_04
Development Phase:	Phase 2a
Sponsor:	Laboratoris Sanifit Europa Building, 2nd floor, 07121 Palma de Mallorca. SPAIN
Principal Investigator:	[redacted]
Study Centres:	[redacted]
Study Objectives:	To evaluate the effect of SNF472 on top of standard of care on promoting wound healing and other parameters of therapeutic response in haemodialysis patients with calciphylaxis (calcific uraemic arteriolopathy, CUA)

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Study Design:	This is an open label, single arm clinical trial to investigate the effect of SNF472 in uraemic calciphylaxis patients, on top of standard of care.
Investigational Medicinal Product:	**SNF472** Presented as 10 mL or 5 mL of sterile liquid in transparent glass vials, containing either 300 mg or 450 mg of SNF472, respectively. The SNF472 solutions used will be either 30 mg/mL (Batch number P00142-L001E) or 90 mg/mL (Batch number PD14081) and will be diluted in a 100-mL saline bag and the contents of the whole bag will be administered to the patient by slow infusion. SNF472 will be administered between 2.5 h and a 4 h period using the dialysis system during the dialysis session.
Number of Patients:	15 evaluable CUA patients who complete the 12-week treatment period. A total of 15 evaluable subjects was determined necessary to show with 80% power that the percentage of subjects for which the primary ulcer is totally or partially healed after 12 weeks of treatment is greater than 25%. For these calculations, it was assumed that the percentage of totally or partially healed subjects for SNF472 will be 60%.
Study Population:	**Main inclusion criteria:** 1. Patients with either newly diagnosed CUA OR recurrent CUA that has been dormant with no skin lesion involvement for at least 90 days from study start (new or recurrent diagnosis must be made within 5 weeks of study start) 2. Patients who signed the written informed consent to participate in this clinical trial (prior to any clinical trial-related procedures being performed), after reading the Patient Information Sheet and Informed Consent Form (ICF), and who had the opportunity to discuss the clinical trial with the Investigator or designee 3. Males or females aged ≥18 4. Patients on maintenance haemodialysis 5. Patients with at least a minimum level of pain on VAS scale or on pain-killers stronger than NSAIDs 6. Females of child-bearing potential should use a highly effective contraceptive measure throughout the study AND have a negative serum pregnancy test at entry. Male patients having sexual relationship in which pregnancy can occur should take adequate contraceptive precautions (wear a condom) (see section 8.3.1.) **Main exclusion criteria:** 1. Body weight above 150 kg 2. BMI >35 and central(abdominal) ulcers 3. History of bisphosphonate treatment within 12 months before entering into the study 4. Severely ill patients without reasonable expectation of survival for > 6 months according to the treating physician

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5. Patients with scheduled parathyroidectomy during the run-in or study period
6. Female patients who are either intending to get pregnant or are undergoing treatment to get pregnant, as well as breast-feeding females
7. Participation in another clinical trial with an experimental drug within 90 days prior the inclusion
8. Any psychological, emotional problems, any disorders or resultant therapy that is likely to invalidate informed consent, or limit the ability of the patient to comply with the Clinical Trial Protocol requirements
9. Patients who, in the opinion of the Investigator, are considered unsuitable for any other reason

Study Procedures:

Written informed consent will be obtained from all patients before any study-related procedures are performed.

The patient's medical history, demographic, and baseline characteristics, as well as a picture of the wound deemed to be CUA, will be collected to determine the patient's eligibility for inclusion, which will be analysed [redacted].

Blood samples taken routinely from patients will be used as source data for the trial.

SNF472 will be administered by infusion at a single, constant dosage for a minimum of 2.5h up to the whole duration of the dialysis session. SNF472 will be administered at three haemodialysis sessions per week for 12 consecutive weeks.

Follow-up assessments including lesion documentation and clinical status will be done at regular intervals (ulcer size, features, Bates-Jensen Wound tool assessment, pain, and Wound QoL) over a period of 12 weeks (see Table 1). Additional assessments will include safety and assessment of pharmacokinetics (PK) and pharmacodynamic (PD) profiles. One sample of blood to measure biomarkers will be taken at the time of PK samples (see Table 1).

During the clinical trial, patients will be monitored closely for any adverse events (AEs).
The time points where blood samples will be taken to evaluate safety, PK, PD, and biomarkers are specified in the Table of Assessments (see Table 1).

Criteria for Evaluation:

Safety:

Safety parameters will include AEs and SAEs, clinical laboratory and haematology, clinical chemistry including plasma electrolytes, 12-lead ECG, and physical examination.

Pharmacokinetics:

Only C_{max} (plasma concentration at the end of drug infusion) will be assessed.

Pharmacodynamics:

Plasma samples collected, at baseline and around the tmax, from all subjects, will be used for exploratory PD assessment by using an in vitro test to assess the propensity for hydroxyapatite crystal formation in plasma.

Biomarker:

Serum samples will be collected at baseline and at the end of the study, frozen, and used for exploratory biomarker assessment. The final list of biomarkers will be decided at a later time point.

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Statistical Methods:

Statistical methods:

All statistical analyses and programming of tables, lists, and figures will be performed [redacted] using the latest available version of SAS® (SAS Institute Inc., Cary, North Carolina, USA).

Safety:

All safety parameters will be summarised by time-point (where appropriate).

Pharmacokinetics:

Individual and mean C_{max} values will be obtained

Pharmacodynamics:

Pharmacodynamia will be assessed by an in vitro method to determine the propensity for hydroxyapatite crystal formation in plasma. For each patient, on-study samples will be compared to baseline assessment and reported as a % inhibition of hydroxyapatite crystal formation compared to baseline.

Biomarkers:

Biomarkers will be assessed once the study is finished

Schedule of Assessments:

For a detailed Schedule and Time of Assessments to be performed during the clinical trial, refer to Table 1.

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Table 1 Schedule of Assessments

	SCR	TREATMENT PERIOD																																			FU
Week	**-2, -1**	**1**			**2**			**3**			**4**			**5**			**6**			**7**			**8**			**9**			**10**			**11**			**12**			**13**
Day		**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	
Informed Consent	X																																					
Demographics	X																																					
Lesions Overview	X																																					
Images Collection	X	X			X						X						X						X						X								X	X
Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight	X																X																					X	
Biopsy (if performed by site)[1]	X																																					
Physical Examination	X																																					X
ECG*	X																																					X
ECG (pre dose & end of infusion)*		X X															X X																					X X	

[1] Biopsy is not an inclusion criterion, but if performed the report and analysis will be documented

* ECG assessment will be performed only at sites with appropriate equipment and trained personnel

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	SCR	TREATMENT PERIOD																																		FU
Week	**-2, -1**	**1**			**2**			**3**			**4**			**5**			**6**			**7**			**8**			**9**			**10**			**11**			**12**			**13**
Day		**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	
Safety Laboratory Assessments[2]	X	X															X																			X	X
PTH[3]		X																																		X	
Potassium, Magnesium, Iron (ferritin/transferrin) and Zinc	X																																				X
Potassium, Magnesium, Iron (ferritin/transferrin) and Zinc (predose & end of infusion)*		X X																																		X X	
Ionised Calcium	X																																				X
Ionised Calcium (predose & end of infusion)*		X X			X X						X X						X X						X X						X X							X X	
Pregnancy Test[4]	X										X												X														X	

[2] These data sets will be used from the routine monthly blood analysis performed on each patient

[3] PTH will be measured using the routine test used in the site. Recommendations are given in Section 7.1.3.

[4] Pregnancy test is to be serum at baseline and urine monthly thereafter

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	SCR	TREATMENT PERIOD																																		FU
Week	**-2, -1**	**1**			**2**			**3**			**4**			**5**			**6**			**7**			**8**			**9**			**10**			**11**			**12**			**13**
Day		**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	
Treatment History (prior medication)[5]	X																																				
Medical History	X																																				
Eligibility[6]	X																																				
CUA Diagnosis	X																																				
Treatment (Intravenous SNF472)[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Wound QoL Score		X															X																				X	
Pain Score (VAS scale)	X	X			X						X						X						X						X								X	X
Lesion Score (BJWAT)		X			X						X						X						X						X								X	X
Biomarkers		X																																			X	
Plasma PK and PD sampling (predose & end of infusion)*		X X																																			X X	

[5] Prior medication includes medications within 6 months of study start

[6] The inclusion/exclusion criteria will be assessed for each patient at Screening – final entry into the study depends on confirmation by the PI, Dr VB

[7] A Treatment Period includes 3 dialysis sessions/week x 12 weeks (36 treatments)

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	SCR	TREATMENT PERIOD																																		FU
Week	**-2, -1**	**1**			**2**			**3**			**4**			**5**			**6**			**7**			**8**			**9**			**10**			**11**			**12**			**13**
Day		**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
End of Study Visit																																						X

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LIST OF STUDY STAFF

This clinical trial will be conducted in US and EU sites.

[redacted]

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2. Sponsor

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[redacted]	

3. Academic Research Organisation (ARO) / Contract Research Organisation (CRO)

[redacted]	[redacted]

4. Independent Committee (Ulcer assessment)

Reference pathologist [redacted]	**Dermatologist** [redacted]

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5. Study Coordination

Scientific Advisor Imaging, Core Reading Lab for main Endpoint (Imaging)	**Study Monitor US**
Data Management	**Study Monitor UK/Spain**
Pharmacovigilance Department	**Statistics**
24-Hour Emergency Contact EU	**24 Hour Emergency Contact USA**

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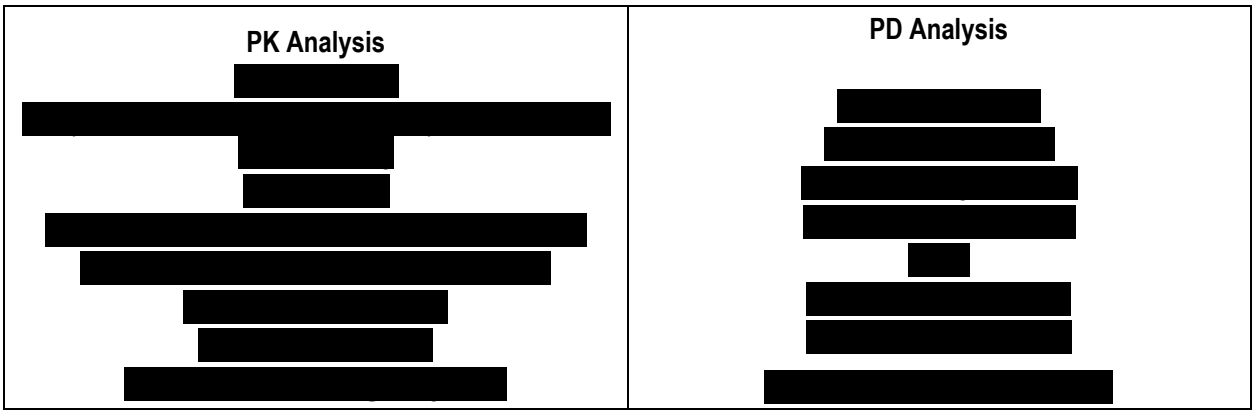
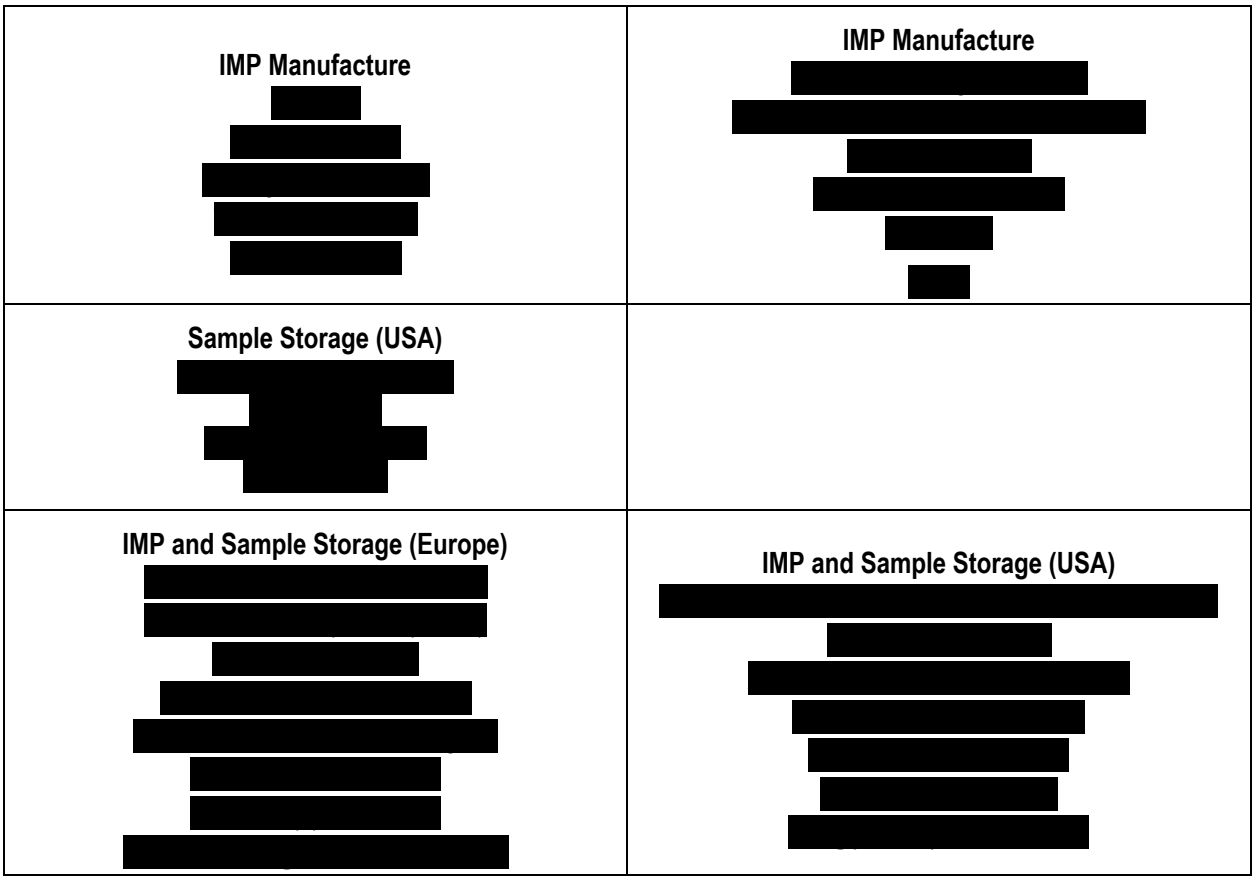
6. PK and PD Laboratory



7. IMP Manufacture, IMP and Sample Storage



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LIST OF TABLES

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARO	Academic research organisation
AST	Aspartate aminotransferase
BWAT	Bates Jensen Wound Assessment Tool
Ca	Calcium
CDISC	Clinical Data Interchange Standards Consortium
C_{max}	Maximum observed plasma concentration
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
CRO	Contract Research Organisation
CS	Clinically significant
CTC-A	Clinical Trial Center-Aachen
CUA	Calciphic Uremic Arteriolopathy
CVC	Cardiovascular calcification
DESC	Dose Escalation Safety Committee
DMP	Data Management Plan
EC	Independent Ethics Committee
ECG	Electrocardiogram
EC50	Effective concentration 50%
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EOS	End of Study
ESRD	End-stage renal disease
EU	European Union
EVG	Elastic-van-Gieson stain
FDA	Food and Drug Administration
Fe	Iron
FU	Follow-Up
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
GRAS	Generally regarded as safe
HAP	Hydroxyapatite
HD	Haemodialysis
hERG	human Ether-a-go-go Related Gene

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HRQOL	Health-Related Quality of Life questionnaire
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMI	Institute of Medical Informatics
IMP	Investigational medicinal product
IP6	Myo-inositolhexaphosphate
IRB	Investigational Review Board
IV	Intravenous
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of patient
NCS	Not clinically significant
NSAID	non-steroidal anti-inflammatory drugs
L	Litre
OTC	Over-the-counter
P	Phosphorus
PET	Polyethylene terephthalate
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
PTH	Parathyroid Hormone
PV	Pharmacovigilance
QT	QT interval
QTc	Corrected QT interval
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Fridericia's formula
RDR	Rare Disease Registries
RWTH	Rheinisch-Westfälische Technische Hochschule
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCR	Screening
SDTM	Standard Data Tabulation Model
SOC	System Organ Class
SOP	Standard operating procedures
STS	Sodium thiosulfate
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
UK	United Kingdom
USA	United States of America

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VAS	Visual analogue scale
WHO-DD	World Health Organisation's Drug Dictionary

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2. INTRODUCTION

2.1. Background

SNF472 is an intravenous (IV) formulation of the hexasodium salt of myo-inositolhexaphosphate (IP6, phytate). It is being developed for the treatment of calciphylaxis, as well as for the prevention of cardiovascular events in patients with end-stage renal disease (ESRD) undergoing haemodialysis (HD).

2.1.1. Properties of Myo-Inositolhexaphosphate

Myo-inositolhexaphosphate is a naturally-occurring substance found in beans, brown rice, corn, sesame seeds, wheat bran, and other high-fibre foods. The calcium salt of IP6 is listed by the Food and Drug Administration (FDA) as generally recognised as safe (GRAS)[1]. It is highly polar and poorly absorbed when given orally. When high oral doses are administered, IP6 has chelating properties in the gastrointestinal lumen preventing the absorption of cations such as calcium, magnesium and iron [2-4]. Due to this property it has been regarded for almost 50 years as an anti-nutrient, because it can reduce the gastrointestinal absorption of mineral oligoelements.

Evidence of the potential health benefits of IP6 has emerged in parallel with advances in the development of analytical tools for its determination in biological fluids and tissues. The physicochemical properties of IP6 in biological systems make it undetectable with most conventional analytical techniques. Its presence in human tissues and body fluids was only shown at the end of the 1990's, after the development of sensitive assay methods[5-8]. In 1996, IP6 levels were shown to be present in human urine[9] and this led to the establishment of a link between IP6 and health, particularly with respect to calcium-related diseases, such as renal stones[10-12], osteoporosis[13-15], and CVC[16-18].

When administering SNF472 to animals as an IV bolus for 28 days, no adverse effects were reported up to 7.5 mg/kg in rats and 10 mg/kg in dogs. At 19 and 30 mg/kg, the observed adverse effects were related to the maximum observed plasma concentration (C_{max}). The clinical signs in animals suggest that the chelation of cations in the blood in rats occurs well above the therapeutic dose levels (2 to 3mg/kg). Moreover, extensive telemetry studies in dogs showed that doses given by bolus, which leads to QTc prolongation, can be given by slow infusion without any effects on ECG parameters, including QTc. QTc prolongation can be reversed giving IV calcium gluconate. To avoid bolus C_{max}-related adverse effects, IP6 will be administered by slow IV infusion during the dialysis session. The IV route achieves higher plasma concentrations of IP6 than is feasible orally and avoids chelation within the gastrointestinal tract.

2.1.2. Evidence for Efficacy in Calcium-Related Diseases

Beneficial properties have been attributed to IP6 in oncology [19-23] and calcium-related diseases (e.g., prevention of renal lithiasis [10-12], osteoporosis [13-15], CVC [16-18], sialolithiasis [24], and dental tartar [25].

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Myo-inositolhexaphosphate has been shown to prevent vascular calcification in a variety of animal models [16-18]. The *in vitro* and *in vivo* results show that SNF472 prevents the formation of hydroxyapatite [26].

Epidemiological data show a negative correlation between physiological IP6 levels and CVC. A high dietary intake of IP6 is associated with a lower incidence of aortic stenosis and aortic valve calcification [27].

The inhibition of pathological processes of calcification in soft tissue by IP6 is accompanied by a positive effect on bone. Both animal models and epidemiologic data suggest that IP6 could be an effective agent for treating osteoporosis by reducing bone mineral density loss. Ovariectomised Wistar rats with an IP6 enhanced diet had reduced loss of bone mineral density caused by oestrogen deficiency [13].

Myo-inositolhexaphosphate has also been shown to inhibit mineralisation *in vitro* of MC3T3-E1 osteoblasts cultures [28]. The potential mechanism is through binding to growing crystals and through induction of osteopontin expression. This data suggest that IP6 may regulate physiological bone mineralisation by directly acting extracellularly and by serving as a specific signal at cellular level for the regulation of osteopontin. When incubating human mesenchymal stem cells (pre-osteoblasts) with IP6, bone formation activity was enhanced [29].

Two epidemiological studies in 1500 and 180 subjects, showed that low IP6 intake was associated with a decline in vertebral and femoral bone mineral density [14, 15]. A recent epidemiological study in 169 post-menopausal women demonstrated that high IP6 exposure over 12 months was associated with lower bone mass loss and decreased fracture risk (lumbar spine and femoral neck)[30].

Sodium phytate is also used for Technetium bone scanning (Fyton; 15 mg Na-phytate [31]). The dose prescribed varies from a minimum of 2.5 mg to a maximum 5.0 mg of 99mTc-phytate. This combination is used in medicine as a source of radiation for radiotherapy and for diagnostic purposes. Published data shows two half-lives: $t_{½}$ α: 2.4-7.0 min, $t_{½}$ β: 69-105 min, with a distribution into bone and liver, and slow disappearance from liver. It is possible that this reflects the half-life of IP6 in humans.

2.1.3. Disease, Coronary Artery Calcification and Events

The prevalence of ESRD in the United States of America (USA) is 661,648 patients [32] and according to the European Renal Association/European Dialysis and Transplant Association Registry, in 2014 the estimated number of new renal replacement therapy patients in the 25 countries of the European Union (EU) was 71 631 [33].There are approximately 360,000 renal replacement therapy patients in the EU, with 66% of them being treated by dialysis and the remainder living with a functioning graft [34].

Calciphylaxis is a rare disease (ORPHA280062) characterised by progressive painful necrotic skin ulcerations and calcification of blood vessels. It occurs mostly, but not exclusively in patients with ESRD and the mean life expectancy is even lower than for haemodialysis patients [35]. The prevalence rate is well below the statutory thresholds for orphan

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diseases of 5/10,000 in the EU (European Medicines Agency) and an overall number of 200,000 patients in the USA (FDA). It affects 1% to 4% of the ESRD population [35].

2.2. Rationale for the Clinical Trial

CUA patients are almost all on dialysis, except for a very small percentage who are non-uraemic. CUA has no specific treatment. Calciphylaxis is a life-threatening condition with a high mortality rate. The overall mortality in calciphylaxis patients with ESRD is 60-80% with a 1 year survival of 45% [35, 36], whereas non-uremic calciphylaxis appears to have a slightly better prognosis with an overall mortality of 52% [37].

The difference between survival curves of cases and controls was most striking in the first year and more specifically in the first few months after the diagnosis of calciphylaxis [38]. It is clear that the progression of calciphylaxis is highly aggressive with early mortality compared to HD patients without calciphylaxis. The mortality of non-uraemic calciphylaxis seems to be about 30% lower than in patients with uraemic calciphylaxis [36, 37].

The pathophysiology of CUA involves the deposition of calcium in the media of small vessels. This leads to regional, extremely painful ischemia leading to ulceration. The lesions tend to appear in the upper and lower limbs, although truncal lesions have also been described. In addition to the pain – requiring opioids to be managed – these patients have an increased susceptibility to infections, which is responsible for over 50% of the mortality. Empirical treatments available include sodium thiosulfate, hyperbaric O2, bisphosphonates, surgical debridement, and other locally implemented initiatives. However, these measures do not seem to improve either the course of the wound(s) or the high mortality rate [39-42]. SNF472, due to its innovative mechanism of inhibition of the final common pathway of vascular calcification, has the potential to decrease the amount of vascular calcification in these patients, hence shortening the time to healing of the wounds and potentially decreasing mortality rates. This study will address the potential of SNF472 to improve the course of the wounds seen in CUA patients.

Further details can be found in the Investigator's Brochure [26].

See Section 4.3 for justification of the clinical trial design.

2.3. Risk-Benefit Assessment

The currently available information of clinical experience with IV IP6 is based on:

1. Technetium formulations for bone and other scans
2. A single ascending dose study of SNF472 in healthy volunteers
3. Both a single and repeated ascending dose study in haemodialysis patients treated for up to 28 days

SNF472 has been extensively studied in non-clinical models for efficacy, safety, pharmacokinetics, and toxicity. The main toxicological finding with SNF472 in animals – at high doses only - is hypocalcaemia due to chelation of ionised

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calcium. The symptoms and signs observed include ECG effects, particularly transitory and reversible QTc prolongation. This is seen at C_{max} values about 100-fold higher than the expected therapeutic levels. The effect is not present in animals when the same bolus doses are administered by slow intravenous infusion. Moreover, SNF472 does not block the hERG channel (Study No SNFSF2010_01 A0189 [43]). The hypocalcaemia and the associated QTc effect are rapidly reversed by intravenous calcium gluconate. It is expected that the risk of associated hypocalcaemia will be minimal in haemodialysis patients, as slow infusions ranging from 2.5 to 4 hours will be used and the plasma calcium concentration is controlled by the calcium content of the dialysis fluid. Furthermore, in the unlikely situation of hypocalcaemia symptoms and signs occurring, they can be reversed by the administration of IV calcium-gluconate.

During the phase I studies with volunteers, single doses from 0.5 mg/kg to 12.5 mg/kg were administered (SNFCT2012_03 Part C). A single dose of 9 mg/kg (SNFCT2012_03 Part C) and repeated doses from one to 20 mg/kg were studied (SNFCT2014_03) in haemodialysis patients. In healthy volunteers, SNF472 was generally well tolerated, except for the occurrence of mild to moderate local infusion site irritation. Infusion site irritation is not an issue in HD patients, as SNF472 is injected into the HD tubing and passes through a volume of blood of at least 200 mL before reaching the patient's blood vessels.

Treatment-emergent adverse events (AEs), assessed as probably related to the IP, were infusion site pain, infusion site erythema, infusion site hypoaesthesia, and infusion site swelling. A single patient on the 9 mg/kg dose developed mild tingling of short duration twice (at 30 minutes and 2 hours) during the infusion. No treatment was required. Treatment-emergent AEs assessed as possibly related to the IP were injection site bruising, headache, dizziness, pain in extremity, lip tingling, and myalgia.

A preliminary analysis of the SAD study suggested that infusion of 5mg/kg, 9mg/kg and 12.5 mg/kg caused increases in QTcB in HVs. These changes mainly occurred within the normal range and values outside the normal range were close to the upper limit of normal. No values were seen above 500 mSec (risk of Torsdes des Pointes). Mechanistically this can be explained by chelation of ionized Ca. It is also clear from limited data currently available that decreased ionized Ca is not a risk in HD patients due to slow infusion of SNF472, dilution of SNF472 in at least 200 cc of blood within dialysis machine tubing prior to entering the blood vessels, and because Ca concentrations are buffered by the Ca content of dialysate fluid across a semipermeable membrane. Overall, the data available suggest a favourable benefit/risk ratio.

2.3.1. Efficacy

Myo-inositolhexaphosphate prevents vascular calcification in non-uremic and uremic animal models. Published studies [16, 17, 44], as well as the non-clinical studies with SNF472 have shown that parenteral IP6 significantly prevents vascular calcification by between 60% and 95% in animal models. The SNF472 efficacy data obtained in animals have helped characterise the concentration-effect relationship and were used to predict potential doses for human clinical

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studies. The maximum therapeutic effect was observed at either a dose of 1 mg/kg in rats in the vitamin D model or plasma levels in the 5000-10000 ng/mL (7.5-15 µM) range, depending on the specific model used.

In animal models of calciphylaxis, where a dystrophic calcification in rat's soft tissues is induced, IP6 clearly reduces plaque formation (calcinosis cutis) induced by $KMnO_4$. Calcification was significantly lower in animals receiving IP6. In rats sacrificed two days after $KMnO_4$ treatment calcified deposits were only found in injured tissues of non-IP6 treated groups (Study No EF2004_10 [45, 46]).

IP6 has also been shown to inhibit mineralisation in vitro of MC3T3 –E1 osteoblasts cultures [28]. The potential mechanism is through binding to growing HAP crystals and by induction of osteopontin expression. When human mesenchymal stem cells (pre-osteoblasts) were incubated with IP6, bone formation activity was enhanced [29].

SNFCT2012_03 Pharmacodynamic Data:

Pharmacodynamic assessments (calcification potential of plasma [47]), in healthy volunteers showed a 80% inhibition at 5 mg/kg SNF472, which appeared to plateau thereafter since the effects were the same for the 9 and 12.5 mg/kg doses.

SNFCT2012_03 Pharmacodynamic Data:

Pharmacodynamic assessments in haemodialysis patients showed an 80% inhibition at 9 mg/kg SNF472.

SNFCT2014_03 Pharmacodynamic Data:

Pharmacodynamic assessments in haemodialysis patients showed an 80% inhibition from 5 mg/kg SNF472 onwards. Less than 20% effect was seen at 1 mg/kg.

2.3.2. Safety

SNF472 was studied in rats and dogs in different toxicology and safety studies, which range from 28 days up to 3 months of treatment.

In the 28-day studies in rats high concentrations produced local irritation. In the 13-week studies, 15-minute daily intravenous administration of SNF472 in rats and dogs induced no mortality and there were no findings attributable to a direct systemic effect of SNF472.

The cardiovascular and respiratory safety pharmacology was assessed in anaesthetised rats and conscious dogs (28-day toxicology and telemetry). In rats, SNF472 did not show any clinically relevant effects on heart rate or blood pressure. In rats and dogs, no effects on respiratory parameters were observed. In dogs, the ECG was evaluated in a 28-day IV (~6-minute bolus) and in a GLP telemetry study. There was a slight heart rate increase in males and females only at the highest dose (30 mg/kg; C_{max}: 359432 ng/mL). These effects appear to be C_{max}-related. In the telemetry

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study SNF472 was administered as long infusion periods (2 hours) and short infusion times (6-minute bolus). Plasma SNF472, calcium, and potassium levels were evaluated. Health status, body weight, cardio-respiratory function, ECG, body temperature, total (serum), and free (blood) concentrations of potassium were not affected by a 2-hour infusion of SNF472 at 3 mg/kg, 10 mg/kg, or 30 mg/kg. QTc prolongation was observed with the 6-minute bolus at 30 mg/kg, but no QTc prolongation was seen with the 2-hour infusion at any of the doses. During the 2-hour infusion, plasma concentrations achieved similar C_{max} values (318180 ng/mL) as with a bolus (although this might be an under-estimation as it is difficult to pinpoint C_{max} after a bolus injection).

Please refer to the Investigators Brochure [26] for further toxicology data.

SNFCT2012_03 Healthy Volunteers Safety data

There were no SAEs, no deaths, and no withdrawals due to AEs during the study. The number of subjects with TEAEs (Treatment emergent adverse event) was similar for all dose groups. TEAEs were mostly mild in intensity and 3 episodes of moderate intensity were reported for the 5.0 mg/kg SNF472 dose and 4 episodes for the 12.5 mg/kg dose.

No clinically significant changes were observed in plasma calcium levels. Although ionised calcium levels were measured, several errors occurred in terms of sampling and analysis:

- As a result of incorrect handling and extraction of samples, the majority of the samples could not be analysed.
- Due to analytical errors, several results in the samples analysed were considered invalid.

The most complete data from ionised calcium set was obtained for the 5 mg/kg dose. In the 12.5 mg/kg dose, there appeared to be a decrease in ionised calcium within the normal range. The baseline values for the other doses were limited. No formal statistical analysis could be done due to the sparse data. In an attempt to get an idea of baseline values in the study populations, we used the ionised calcium before the infusion of placebo or active drug was started, as well as the 12-hour values (8 hours after C_{max} at a time when no SNF472 was detectable in the blood) and we compared with values obtained around t_{max} and per dose. Hence, the ionised calcium concentrations seem to be similar to the pooled baseline values with 5 mg/kg of SNF472. With the 9 mg/kg dose, the two available values seem to be at the lower end of the distribution of baseline values, whereas with 12.5 mg/kg dose, two of the three available values are below the baseline values. The data, although sparse, suggest that there possibly was a dose-related decrease in ionised calcium.

There were, however, no clinical features of hypocalcaemia or clinically relevant increases in QTc observed with any of the three doses evaluated. SNF472 concentrations achieved with 12.5 mg/kg were around eight-fold higher than the anticipated therapeutic concentrations.

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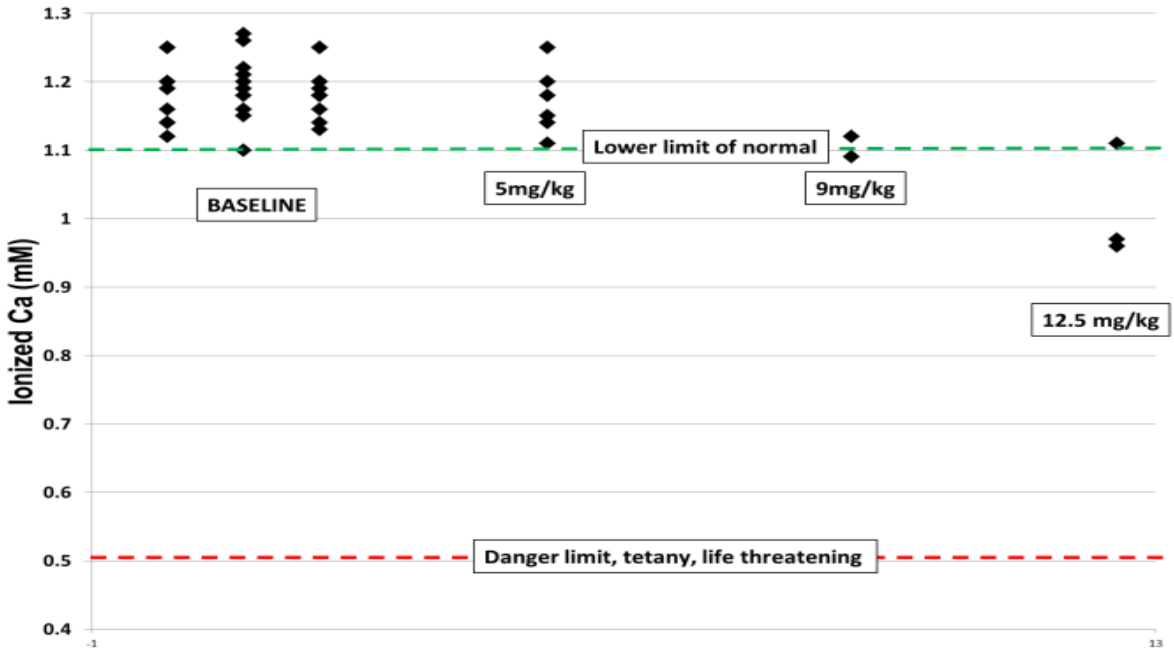

Figure 1 Ionised calcium concentration at the time of peak concentrations with each dose compared to baseline.

Baseline values are a (placebo pre-dose and at 12 hours, b (active treatment pre-dose) and c (active treatment at 12 hours). (mmol/L). Green line: Normal range:1.17-1.30 mmol/L. Red line: 0.5 mmol/L: possibility of tetany and potentially life-threatening

The planned doses in the protocol were 0.5, 1.5, 5, and 10 mg/kg. PK simulation based on preclinical data predicted plasma concentrations (C_{max}; ng/mL) of 3000, 10000, 30000 and 70000 respectively. After the 1st cohort (0.5 mg/kg), the DESC (Dose Escalation Safety Committee) decided to increase the dose to be tested in the 2nd cohort (1.5 mg/kg) to 5 mg/kg. This decision was based on PK results showing much lower values than the anticipated systemic exposure of around 2500 ng/mL as predicted by the PK model (levels were below the limit of quantification of 500 ng/mL). According to new PK estimations, 5 mg/kg was expected to produce the initially expected level of exposure with 1.5 mg/kg. The C_{max} with 5 mg/kg was 11571 ng/ml, which is nearly triple the anticipated EC50. Using the PK data of the 5 mg/kg dose and the safety data after each cohort, the DESC decided to modify the following two doses to reach the target concentrations. The doses of 9 and 12.5 mg/kg produced SNF472 plasma levels of 24394 and 42207 ng/mL, respectively.

SNFCT2012_03 and SNFCT2014_03 Haemodialysis Patients. Safety data

The single dose study in haemodialysis patients (SNFCT2012_03) and up to 28-day MAD study in haemodialysis patients (SNFCT2014_03). Both have been finalised. The dose range explored in these 2 studies was between 1 mg and 20 mg/kg, and in the MAD 10 mg/kg was administered 3 times a week for one month. Although unblinded, the data are still being analysed, the PK results suggest dose-linearity, no accumulation, and an exposure at 20 mg/kg in the range of 68000 ng/mL. Expected therapeutic levels are around 5000 ng/mL. The preclinical safety margin is

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established in 127291 ng/mL. No significant safety and tolerability issues were reported. One single SAE was observed, not related with the drug.

As a conclusion for Phase 1 clinical trials performed with SNF472 up to date: treatment-emergent adverse events seen exclusively in healthy volunteers and not in HD patients, and assessed as probably related to the investigational medicinal product (IMP), were infusion site pain, infusion site erythema, infusion site hypoesthesia, and infusion site swelling. Treatment-emergent adverse events, assessed as possibly related to the IMP, were injection site bruising, headache, dizziness, pain in extremity, eyelid injury, and myalgia. These effects were not seen in HD patients. A single SAE was recorded and was not related to treatment. No clinical significant effects were observed on vital signs, or in the laboratory tests. ECGs, including the QTc interval, was fully evaluated and no clinically significant effects were observed. It showed the following:

- QTcB prolongation in HV was found (all values were below 450 msec). Sparse ionised calcium data suggested mild hypocalcaemia, correlating with QTcB
- QTcB prolongation in HD patients occurred with active as well as placebo treatment. It was not associated with hypocalcaemia and a relationship to chelation of calcium can be ruled out

QTc changes are often seen in HD patients and can be due to the composition of the dialysis fluid, underlying cardiovascular disease, changes in Ca, Mg, or K, or due to medication. As HD patients showed no significant decreases in ionized Ca, SNF472 does not affect hERG channels and QTcB prolongations also occurred in placebos; an SNF-related effect is therefore highly unlikely.

2.3.3. Galenics

SNF472 administered i.v. is 100% bioavailable. No compliance issues will be expected with the IV route in patients who undergo regular dialysis.

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3. STUDY OBJECTIVES

This is an open label, single arm clinical trial to investigate the effect of SNF472 in uraemic calciphylaxis patients, on top of standard of care. The study objective is to evaluate the effect of SNF472 on top of standard of care on promoting wound healing and other parameters of therapeutic response in haemodialysis patients with CUA. “Standard of care” of calciphylaxis is not defined by evidence or guidelines. However, experts in the field suggest a personalised management plan for each patient based on a list of potential measures which have recently been summarized [39, 41].

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4. OVERALL DESIGN AND PLAN OF THE STUDY

4.1. Overview

[redacted] To reach the study objectives, 15 evaluable CUA patients who complete the 12-week treatment period will be enrolled

[redacted] will be responsible for the diagnosis of CUA together with the locally treating physician at the study site (team decision, two-pairs-of-eyes decision). The decision to include the patient into the study should be made based on the following criteria [48]:

- The diagnosis of calciphylaxis can be made when:
  1. The following clinical features are all present, or
  2. Two of the following clinical features and typical histopathological findings are present
- Clinical features:
  1. A patient on chronic haemodialysis or haemofiltration or haemodiafiltration for chronic kidney disease
  2. More than 2 painful and non-treatable skin ulcers with concomitant painful purpura
  3. Painful and non-treatable skin ulcers on the trunk, extremities, or penis with concomitant painful purpura
- Histopathological findings:

  Skin biopsy is recommended only if the three clinical findings presented above are not present and will be left to the discretion of the treating physician. Typical histopathological findings of the skin are as follows:

  - Necrosis and ulceration of the skin with calcification of the tunica media and internal elastic membrane of small to medium-sized arterioles of dermis and subcutaneous fat
  - Concentric stenosis due to oedematous intimal thickening of the small to medium-sized arterioles of dermis and subcutaneous fat

Intense pain as primary manifestation followed and associated with cutaneous lesions and palpation of firm calcified (leather-like) subcutaneous tissue surrounding the lesion is suggestive of calciphylaxis. Typically, the lesions do not occur at sites primarily affected by venous insufficiency or arterial malperfusion. In view of the painful character of the lesions, palpation is left to the discretion of the treating physician.

The diagnosis of calciphylaxis can be supported by findings obtained from a skin biopsy. Benefits of a biopsy include exclusion of other conditions that can mimic calciphylaxis such as vasculitis. The characteristic histological features of calciphylaxis include calcification, microthrombosis, and fibrointimal hyperplasia of small dermal and subcutaneous

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arteries and arterioles, leading to cutaneous ischemia and intense septal panniculitis. Von Kossa or Alizarin red staining are required to detect micro calcification. [redacted] [39-41].

Performing a skin biopsy will be left to the discretion of the treating physician and will be performed following the site's SOPs. In case the biopsy is performed as a routine procedure at the site, and the result is positive for CUA, the patient is included – as long as the "gatekeeper", [redacted] agrees with the remaining diagnostic parameters. If the biopsy is negative, [redacted] will check the biopsy results and will decide if he agrees or disagrees with the remaining diagnostic parameters to include or not the patient.

In order to have readable biopsies, the following requisites need to be fulfilled:

1. site of biopsy: the biopsy should include the ulcer borders, not the necrotic core, and be deep enough to show deep skin layers
2. the biopsy material should be fixed in either formalin or paraformaldehyde or glutaraldehyde
3. paraffin blocks should be mailed to the core pathology lab [redacted] where appropriate stains such as EVG, von Kossa, etc. will be performed

Wound treatment of calciphylaxis ulcerations will be performed according to local good clinical practice SOPs of the corresponding clinical site irrespective of the fact that the ulceration might be evaluated as treatment target within the trial. Such a wound treatment SOP might include the interdisciplinary team approach by nephrologists, dermatologists, (plastic) surgeons, and specialized nurses.

4.2. Endpoints

4.2.1. Primary endpoint

- The primary lesion is the largest one – based on longitudinal and transverse measurements - and the one to be followed through imaging throughout the duration of the study by taking pictures of the lesion (more details concerning the imaging of the lesions will be addressed in the imaging manual)
- A maximum of 3 lesions – including the primary one – will be thoroughly assessed during the study
- Lesion score (Bates-Jensen Wound Assessment tool [49]) will be performed during Weeks 1, 2, then 4, 6, 8, 10, 12, and EOS (FU) visit. Of note, elements of the Bates-Jensen Wound Assessment tool which imply probing the wound or measuring its depth are left to the discretion of the treating physician at the site and are not compulsory

4.2.2. Secondary endpoints

- Wound infection, both for the primary and the secondary lesions

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- Systemic infection
- Surgical treatment of the wound
- Hospitalisation defined as being admitted for >24 hours
- Course of the secondary lesions defined clinically as for the primary [49]
- Change in pain from week 0 to 12 according to 100 mm Visual Analog Pain Scale (VAS)
    - Pain scale done at Screening, weeks 1, 2, 4, 6, 8, 10, 12, and EOS (FU) visit
- Change in dose and type of pain medication assessed as a continuous variable. Name (INN), dose, and number of pills captured.
- Wound QOL score done at Screening and weeks 1, 6, and 12
- Death

4.3. Justification of the Clinical Trial Design

Preclinical data with SNF472 supports the hypothesis that the compound is able to prevent cardiovascular calcification (CVC). Calciphylaxis is a rare condition with a high mortality rate. It is characterised by progressive painful, necrotic, skin ulcerations, and calcification of blood vessels. It occurs mostly (98% of cases), but not exclusively, in patients with ESRD, where it is also referred to as Calciphic Uremic Arteriolopathy (CUA). “Standard of care” of calciphylaxis is not defined by evidence or guidelines. However, experts in the field suggest a personalised management plan, taken from each calciphylaxis patient a personalized selection from a homogenous list of measures to be taken which have recently been summarized [39, 41]. Since there is no standard of care and one-year mortality rates are about 50% -in a year, the study is open-label and has no placebo control arm.

Phase 1 clinical trials with SNF472 have been completed in healthy volunteers and in patients on haemodialysis. The impact of renal failure and the effect of dialysis on the PK of SNF472 have been assessed, both in single and multiple dosing and up to one month of treatment. Calciphylaxis patients are HD patients; hence SNF472 is expected to have the same PK/PD and safety features.

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5. STUDY POPULATION

The clinical trial population will consist of male or female HD patients diagnosed with CUA, who are 18 years or older. Participants must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria.

The Investigator will be required to keep a record of patients who were considered for enrolment but not enrolled, e.g., patient screening log, according to local procedures. This information is necessary to establish that the patient population is selected without bias.

5.1. Number of Patients

It is planned to include 15 male or female CUA patients who complete the 12-week treatment period.

Patients who leave the clinical trial before being entered into the study will be considered as screening failures and will always be replaced. Therefore, sufficient reserve patients should be recruited, where possible. Patients withdrawn after dosing may be replaced as needed to obtain 15 patients who complete the 12-week treatment period.

See Section 9.5 for a discussion of sample size.

5.2. Recruitment

For this study, both non-hospitalised and hospitalised calciphylaxis patients will be recruited after obtaining written informed consent, with a preference for non-hospitalised patients, wherever possible.

Patients will be approached to participate in the study during the Screening period.

5.3. Inclusion Criteria

Patients who meet the following criteria will be considered eligible to participate in the clinical trial:

1. Patients with either newly diagnosed CUA OR recurrent CUA that has been dormant with no skin lesion involvement for at least 90 days from study start (new or recurrent diagnosis must be made within 5 weeks of study start)
2. Patients who signed the written informed consent to participate in this clinical trial (prior to any clinical trial-related procedures being performed), after reading the Patient Information Sheet and Informed Consent Form (ICF), and who had the opportunity to discuss the clinical trial with the Investigator or designee
3. Males or females aged ≥18
4. Patients on maintenance haemodialysis
5. Patients with at least a minimum level of pain on VAS scale or on pain-killers stronger than NSAIDs

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6. Females of child-bearing potential should use a highly effective contraceptive measure throughout the study AND have a negative serum pregnancy test at entry. Male patients having sexual relationship in which pregnancy can occur should take adequate contraceptive precautions (wear a condom) (see Section 8.3.1.)

5.4. Exclusion Criteria

Patients who meet one or more of the following criteria will not be considered eligible to participate in the clinical trial:

1. Body weight above 150 kg
2. BMI >35 and central(abdominal) ulcers
3. History of bisphosphonate treatment within 12 months before entering into the study
4. Severely ill patients without reasonable expectation of survival for > 6 months according to the treating physician
5. Patients with scheduled parathyroidectomy during the run-in or study period
6. Female patients who are either intending to get pregnant or are undergoing treatment to get pregnant, as well as breast-feeding females
7. Participation in another clinical trial with an experimental drug within 90 days prior the inclusion
8. Any psychological, emotional problems, any disorders or resultant therapy that is likely to invalidate informed consent, or limit the ability of the patient to comply with the Clinical Trial Protocol requirements
9. Patients who, in the opinion of the Investigator, are considered unsuitable for any other reason

5.5. Patient Withdrawal and Replacement

A patient is defined as having entered the clinical trial when he/she has provided written informed consent. A withdrawal is a patient who receives a study patient code and for whom treatment is prematurely terminated for any reason.

Possible reasons for withdrawal of a subject from the clinical trial:

- Subject does not fulfil inclusion criteria
- AE(s)
- Withdrawal of consent
- Subject lost to follow-up
- Protocol violation
- Pregnancy
- Other reasons as judged by the investigator (see also **7.1.4** 12-Lead Electrocardiogram abnormalities)

Patients may withdraw consent for participation in the clinical trial at any time without penalty and for any reason without prejudice to his or her future medical care. The patient does not need to give a reason for withdrawal of consent. The

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Investigator is also free to terminate a patient's involvement in the clinical trial at any time, if the patient's clinical condition or non-compliance warrants it. The Sponsor or the Regulatory Authorities may request termination of the clinical trial if there are concerns about study conduct or safety.

In all cases, the reason(s) for withdrawal and the primary reason or failure to provide a reason, must be recorded in the Case Report Form (CRF).

If a patient is withdrawn, or chooses to withdraw, from the clinical trial for any reason, the Investigator must make every possible effort to perform the evaluations described for the End of Study Visit (see Section 8.2.5) or to verify the health status of the patient by calling the national death registry. Withdrawn patients may not re-enter the clinical trial.

Entered patients who leave the clinical trial before receiving a study patient code will be considered as screening failures and will be replaced.

Patients who are withdrawn from the study may be replaced at the discretion of the Sponsor and Principal Investigator. Replaced patients will receive the whole treatment.

All patients who experience a clinically significant AE (in the opinion of the Investigator) which is ongoing either at the time of withdrawal or at the End of Study Visit, will be followed up at appropriate time intervals until the AE is resolved to the satisfaction of the Investigator. Since it is unpredictable how long such a follow-up will take, data from this follow-up generated after study finalization will be recorded by the Investigator in the source documents and reported to the Drug Safety and Pharmacovigilance department, but not necessarily collected in the CRF and the database. However, full details regarding this follow-up will be described in the Clinical Study Report.

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6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1. Identity of the Investigational Medicinal Products

Information regarding the dosage form, appearance, and manufacturer of the IMP are presented below:

<table>
<tr><td></td><td>SNF472</td></tr>
<tr><td>Code name:</td><td>SNF472</td></tr>
<tr><td>Description:</td><td>Transparent</td></tr>
<tr><td>Presentation:</td><td>Liquid</td></tr>
<tr><td>Strength:</td><td>30 mg/ml or 90 mg/ml</td></tr>
<tr><td>Dose:</td><td>Dose will be adjusted by body weight.

To simplify logistics, body weights will be divided into 4 body weight categories, in order to homogenise the exposure of patients to the drug. The body weight used to classify the subject into the four categories will be only the dry body weight from the Screening visit.

The dose will be as follows:

<table>
<tr><th>Category</th><th colspan="2">Patient Body Weight Range (kg)</th><th>Total Dose (mg) per patient</th></tr>
<tr><td>1</td><td>50</td><td>65.9</td><td>400</td></tr>
<tr><td>2</td><td>66</td><td>80.9</td><td>450</td></tr>
<tr><td>3</td><td>81</td><td>110.9</td><td>700</td></tr>
<tr><td>4</td><td>111</td><td>150</td><td>900</td></tr>
</table>

All details of the procedure are described in the Pharmacy Manuals for each concentration.</td></tr>
</table>

[redacted] SNF472 will be stored and shipped to either the Pharmacy Services at the Clinical Units or directly to the Clinical Units.

6.2. Dose Rationale

The dose selected has a range of 5.6 mg SNF472/kg to 9 mg SNF472/kg depending of subject weight. This dose range was well tolerated in Phase 1 clinical trials (SNFCT2012_03 and SNFCT2014_03), and is selected to be the anticipated

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therapeutic dose, reaching concentrations to be at the plateau of the PK/PD relationship (see SNFCT2014_03 CSR). To adjust the dose per kilogram, subjects are divided into 4 body weight categories (see Pharmacy manual for details).

Dose levels of SNF472 from 1 to 20 mg/kg were tested in Phase1b/2 trials (SNFCT2014_03) for 1 week and 10 mg/kg for 1 month, without any AE/SAE related with the compound. Cmax values expected at the dose selected are not exceeding (6-fold below) the Cmax of 127,291 ng/mL, which was the NOAEL concentration determined in dog pre-clinical studies.

6.3. Supply, Packaging, Labelling and Storage

The IMP at [redacted] B&C] will be stored in accordance to with the manufacturer's instructions (-20ºC). The IMP will be labelled according to the applicable local health authority, FDA and EMA requirements. [redacted] will send the IMP to the Clinical Unit. All IMP shipments will be carried out on dry ice.

All supplies of SNF472 must be stored on site at 5ºC (±3ºC). The preparation of the patient doses will be described in the Pharmacy Manual. There will be two Pharmacy Manuals, one for the 30 mg/ml vials and another for the 90 mg/ml vials. The 30 mg/ml vials are packaged in boxes of 9 vials. The 90 mg/ml vials are packaged in boxes of 3 vials.

6.4. Drug Accountability, Dispensing and Destruction

The Investigator is responsible for maintaining accurate accountability records of the IMP throughout the clinical trial.

Each administration of the IMP will be documented in the CRF.

The Investigator is responsible for returning all unused or partially used IMP to the Sponsor or overseeing the destruction of unused IMP. The IMP return or destruction will only occur after the drug accountability has been performed, and any discrepancies there may have been resolved by the Clinical Units.

6.5. Patient Identification

At the Screening, each patient will be identified using a unique Identification Number.

Each patient will receive a Patient ID on Day 1 (of the Treatment Period) after eligibility for the clinical trial has been confirmed. The first two letters will correspond to the country where the Clinical Unit is located, the next two/three digits will correspond to the Clinical Unit and the last two/three digits will correspond to the patient.

Patients who withdraw or are withdrawn from clinical trial participation for any reason, regardless of whether IMP was administered or not, will retain their Patient ID and the patient will not be allowed to re-enter the clinical trial.

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6.6. Administration of Investigational Medicinal Products

The IMP administration will consist of a single IV dose of SNF472 over a minimum of 2.5 and a maximum of 4-hour period during the patient's dialysis session. A minimum of 2.5 h of infusion is required.

The exact infusion starting and stopping times will be recorded in the CRF.

The appropriate volume of the investigational product will be administered as a constant rate IV infusion using a 100 mL bag of saline connected directly to the dialysis machine via an IV giving set, but always BEFORE the dialysis filter. The constant rate IV infusion will be carried out using an infusion pump for saline bags. SNF472 should NOT be administered directly intravenously.

The type of dialysis machine used will be documented in the CRF. The method of administration will be as follows:

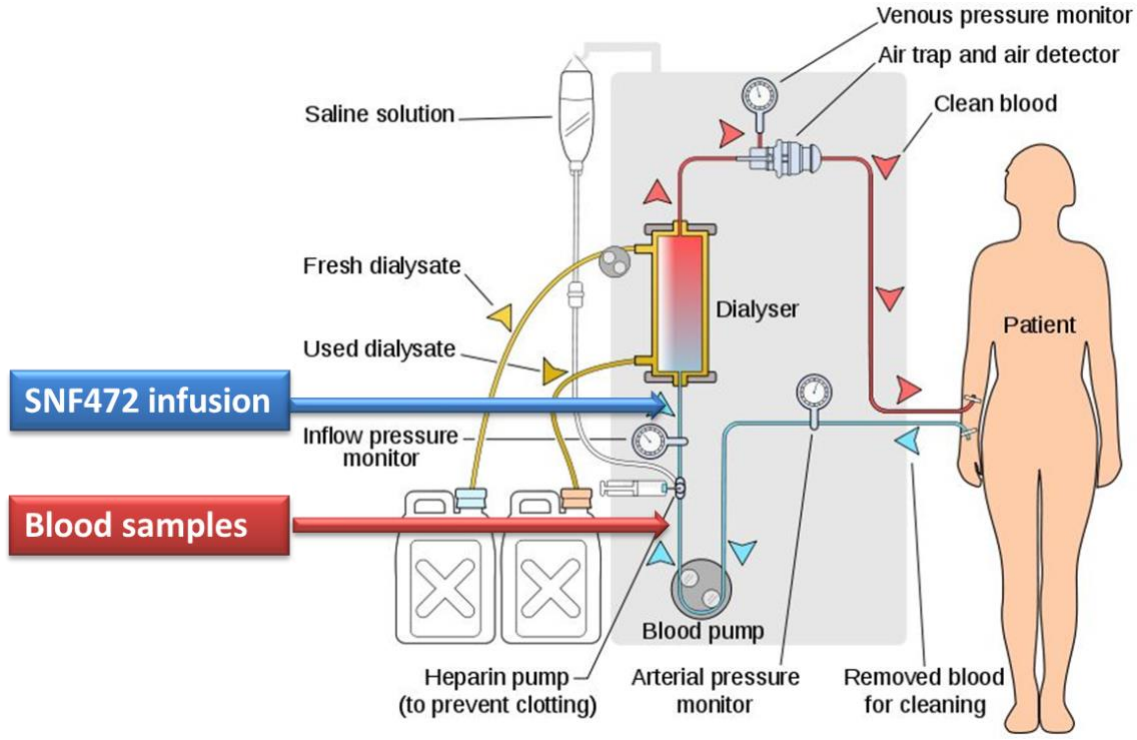

Figure 2 Cartoon of the method of administration including the dialysis machine.

[redacted]

Any dosage interruptions will be recorded in the CRF (i.e., infusion stop and start times). In case there is an interruption of the infusion, once the infusion is re-started, the aim should be to deliver the whole dose, even if this takes longer than originally planned.

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6.7. Compliance

The Principal Investigator or designees will administer/oversee the administration of all IMPs. In addition, the following measures will be taken to ensure treatment compliance:

- The Investigator will attempt to enrol subjects able to understand and comply with the clinical trial
- The exact day and the starting and stopping IMP infusion times will be recorded in the CRF
- The Investigator will maintain accountability records showing the quantities of IMPs received at the Clinical Unit and dispensed to each patient

Any unused IMP, including empty, or partially used containers will be accounted for and returned to the manufacturing site for destruction after obtaining written Sponsor approval.

6.8. Concomitant Medications

6.8.1. Prior and Concomitant Medication

Any medicinal products, prescribed, or OTC taken by a patient other than the IMPs, are considered concomitant medication.

At screening, the patients' medical history and drug history will be recorded in the CRF under the medical history and treatment history sections. The drug history of the patient will include all medications taken in the last 6 months prior to study start. After screening, all medication (along with their daily dosage, duration, and reasons for administration) taken by patients will be recorded in the CRF under the concomitant medication section.

At each subsequent clinical trial visit, patients will be asked about what concomitant medications they have taken since the last visit. Any changes in the dose or dosing regimen of the concomitant medication must be recorded in the CRF.

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7. VARIABLES AND METHODS OF ASSESSMENT

Refer to Table 1 for information regarding when each assessment will be performed.

For this clinical trial, a paper CRF will be utilised for data collection at the clinical sites. [redacted]

At baseline and for inclusion criterion purposes, several pictures of the main wound can be taken and emailed to the study PI so that he can decide which one is the one to be designated as "the" main wound. In following visits, the same wound has to be imaged so that the course of the wound can be assessed.

Image analysis software will be used. Each patient will have a personalised colour reference card with a unique barcode. This card should be placed next to the skin lesion before the image is taken, so that all wound images can be normalised in geometry, colour, and contrast in order to support quantitative measurements. The pictures of the wounds, primary, secondary, and tertiary, will be transferred to the database where they can be easily linked to their corresponding visit.

7.1. Safety Variables

7.1.1. Medical History, Demographic, and Anthropometric Information

The medical history comprises:

- Previous illnesses and surgical procedures
- Family history
- History of drug and alcohol abuse

The treatment history will include all medication the patient has taken or is currently taking up until the Screening visit.

The following demographic and anthropometric information will be recorded at the Screening Visit:

- Age
- Sex
- Race (Caucasian, Hispanic, African-American, Asian or other)
- Ethnicity (Latino or Hispanic, non-Latino or non-Hispanic)
- Body weight (dry weight), without shoes (kg) (if without shoes is not possible then same conditions at each body weight measurement)

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7.1.2. Adverse Events

7.1.2.1. Management of Adverse Events

The Investigator will carefully monitor each patient for AEs. In addition, the information on AEs will be obtained by regular questioning of each patient by the clinical trial staff. No leading questions should be asked. When an AE occurs, the Investigator will decide whether to withdraw the patient from the clinical trial and/or initiate appropriate treatment.

In the case of any event requiring medical intervention occurring during the Treatment Period, the Investigator will institute general supportive measures including, where necessary, respiratory assistance and cardiopulmonary resuscitation.

7.1.2.2. Definitions

An adverse event (AE) is any unfavourable and unintended sign, symptom, or disease that appears or worsens in a subject or clinical investigation subject during the period of observation in a clinical study.

The adverse event may be any of the following:

- A new illness,
- An exacerbation of a sign or symptom of the underlying condition under treatment or of a concomitant illness (including abnormal laboratory finding)
- Unrelated to participation in the clinical study or an effect of the study medication or comparator drug, or
- A combination of one or more of the above factors.

No causal relationship with the study medication is implied by the use of the term “adverse event.” An exacerbation of a pre-existing condition/illness is defined as a more frequent occurrence or as an increase in the severity of the pre-existing condition/illness during the study. Planned or elective surgical or invasive procedures for pre-existing conditions that have not worsened are not adverse events. However, any complication that occurs during a planned or elective surgery is an adverse event. (If the event fits the seriousness criteria, such as an extended hospitalisation, it will be considered a serious adverse event.) Conditions leading to unplanned surgical procedures may be adverse events.

In order for the Sponsor to collect additional information about the clinically important laboratory or diagnostic tests (eg, blood, urinalysis, ECG, imaging) abnormalities, at a minimum, the following abnormalities should be captured on the AE CRF:

- Any test result that meets the criteria for a SAE
- Any test abnormality that suggests a disease and/or organ toxicity that is new or has significantly worsened
- Any test abnormality that required the subject to have study medication discontinued or interrupted

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- Any test abnormality that required the subject to receive specific corrective therapy, close observation, more frequent follow-up assessment, or further diagnostic investigation

Laboratory test abnormalities may not be of clinical significance in the absence of:

- Clinical symptoms
- Change in lifestyle
- Need for intervention

Only clinically significant test abnormalities should be reported as AEs. Determination of the clinical significance of test abnormalities is the responsibility of the Investigator. In particular, Grade 1 or 2 haematology, chemistry, abnormalities should be carefully considered for clinical relevance by the Investigator, as they are less likely to be of clinical significance as compared to Grade 3 or Grade 4 abnormalities. Haematology and chemistry abnormalities determined to be clinically relevant will be assigned a severity rating by the Investigator. A clinical diagnosis, rather than the changes in laboratory or other assessment should be recorded on the CRF as appropriate (eg, anaemia versus low haemoglobin value, bundle branch block rather than abnormal ECG).

All AEs, including intercurrent illnesses, occurring during the clinical trial will be documented in the CRF. Concomitant illnesses that existed prior to entry into the clinical trial will not be considered AEs unless they worsen during the Treatment Period. Pre-existing conditions will be recorded in the CRF on the Medical History or appropriate page.

7.1.2.3. Assessment of Adverse Events

The Investigator will assess each AE according to the categories discussed in the sections below.

7.1.2.3.1. Seriousness

A SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening; this means that the patient was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires hospitalisation or prolongation in existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or a birth defect
- Is an important medical event that may not result in death, be life threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

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Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Note that an AE or suspected adverse reaction is considered "life-threatening" for reporting as an SAE if, in the view of either the Investigator or the Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

The following events do not meet the definition of an SAE with regard to hospitalization: planned hospitalization for a condition present prior to the subject's enrolment in the study, hospitalization of the subject for compliance/convenience reasons, planned hospitalization for an elective medical/surgical procedure, scheduled treatments, or routine check-ups, or a hospitalization or an emergency room visit lasting less than 24 hours.

7.1.2.3.2. Intensity

The Investigator will assess the severity of AEs according to the following definitions:

- Grade 1 (Mild): asymptomatic or transient, short in duration (< 1 week), no change in lifestyle, and/or no medications required.
- Grade 2 (Moderate): symptomatic, duration (1 to 2 weeks), alters lifestyle occasionally, medication relieves symptoms (may be prescription), and/or study medication is continued.
- Grade 3 (Severe): prolonged symptoms, reversible, major functional impairment; prescription medications provide partial relief; may be hospitalized < 24 hours; temporary or permanent study medication discontinuation.
- Grade 4 (includes Life threatening): at risk of death; substantial disability, especially if permanent; hospitalized > 24 hours; permanent study medication discontinued.

7.1.2.3.3. Causality

The Investigator will assess the causality/relationship between the IMP and the AE and record that assessment in the CRF. The most likely cause of an AE/SAE (e.g., disease under treatment, concomitant disease, concomitant medication, other) will be indicated in the CRF with details of the concomitant disease, medication, or other cause.

The causal relationship of the AE to IMP will be described in terms of:

- Possible: the AE:
    - Follows a reasonable temporal sequence from administration of the IMP

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- Could be reasonably explained by the patient's clinical state, environmental or toxic factors or other therapies administered to the patient
- Follows a known pattern of response to the IMP

- Unlikely: the AE:
  - Does not follow a reasonable temporal sequence from administration of the IMP
  - Could be reasonably explained by the patient's clinical state, environmental or toxic factors, or other therapies administered to the patient
  - Does not follow a known pattern of response to the IMP
  - Does not reappear or worsen upon re-challenge
- Not related:
  - The AE does not meet the above criteria
  - There is sufficient information that the aetiology of the AE is not related to the IMP

The relatedness of SAEs will also be assessed and documented on the appropriate CRF page.

7.1.2.4. Recording of Adverse Events

Adverse events will be collected from the time a patient signs the ICF until the Follow-up Visit.

All AEs, regardless of the relationship to IMP, must be recorded in the source documents (e.g., medical record) and will be recorded on the appropriate CRF pages, and documents provided by the Sponsor.

All AE reports should contain a brief description of the event, date, and time of onset, date and time of resolution, intensity, treatment required, relationship to IMP, action taken with the IMP, outcome, and whether the event is classified as serious.

Serious adverse events should be collected for up to 30 days after the last dose of the IMP for subjects unless the subject has withdrawn consent. This could be collected as a phone call.

7.1.2.5. Reporting of Serious Adverse Events

All SAEs that occur during the period of observation (from the first administration of the IMP until the Follow-up Visit) whether considered to be associated with the IMP or not, must be reported within 24 hours after knowledge of the SAE by email or fax to the Pharmacovigilance Department.

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The minimal information required for an initial report is:

- Sender of report (name, address of Investigator)
- Protocol number
- Patient identification (Patient ID, initials, NOT patient name)
- Full description of SAE
- Details of the IMP
- Investigator Causality assessment

However, as far as possible all points on the SAE form should be covered in the initial report and the completed SAE form must be emailed to the Pharmacovigilance Department ([redacted]). In addition, the SAE must be documented in the CRF and documents provided by the Sponsor.

In case the Pharmacovigilance Department cannot be contacted (e.g., after business hours or on weekends), an automated reporting service is available. The required information should be faxed and a message should be left on the voicemail service.

A 24-hour emergency contact will be available during the conduct of the clinical trial. For medical emergencies, the following phone number will be available:

[redacted]

After receipt of the initial report, the Pharmacovigilance Department will review the information and, if necessary, contact the Investigator to obtain further information for assessment of the event. The Investigator will be responsible for informing the local Ethics committee (EC)/ Independent Review Boards (IRB), and central IRB as per local EC/IRB and central IRB requirements. The Sponsor, will be responsible for informing all Regulatory Authorities and the Investigators (if applicable), of findings that could adversely affect the safety of subjects or impact the conduct of the study and will report to regulatory authorities in conformity with expedited and periodic reporting requirements.

Details for the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) can be found in Section 7.1.2.7.

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7.1.2.6. Follow-up of Adverse Events

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved, any abnormal laboratory values have returned to baseline or stabilised at a level acceptable to the Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up.

7.1.2.7. Suspected Unexpected Serious Adverse Reactions

Any AE that is serious or associated with the use of the IMP and SUSARs have additional reporting requirements, as described below:

- If the SUSAR is fatal or life-threatening, associated with the use of the IMP, and unexpected, Regulatory Authorities, the EC/IRB, and Investigators will be notified within 7 calendar days after the Sponsor learns of the serious adverse event. Additional follow-up (cause of death, autopsy report, hospital report) information will be reported within an additional 8 days (15 days in total)
- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with the use of the IMP, and unexpected, Regulatory Authorities, the EC/IRB and the Investigators will be notified within 15 calendar days after the Sponsor learns of the serious adverse event

The Sponsor will also provide annual safety reports to the Regulatory Authorities and the EC responsible for the clinical trial. These updates will include information on SUSARs and other relevant safety findings.

7.1.2.8. Periodic Independent Safety Monitoring

An independent medical monitor will evaluate the totality of safety information collected in the trial at the following time points: 1) when the first 5 patients have completed a full 12 weeks of treatment; 2) when the first 10 patients have completed a full 12 weeks of treatment; and at End of Study. The independent medical monitor will be appointed prior to the first time point and will be a qualified individual who is not directly involved in study conduct and is not a direct employee of the Sponsor or any Principle Investigator in the study.

7.1.2.9. Pregnancy

If a female clinical trial participant or a female partner of a male clinical trial participant who has been exposed to the IMP becomes pregnant, the course and outcome of the pregnancy should be monitored and documented. Pregnancy is not an AE; however, the Investigator should inform the Sponsor immediately of the pregnancy by submitting a completed SAE report form (for tracking purposes) and provide any available follow up information on the Pregnancy Outcome Report Form, including perinatal and neonatal outcome. Protocol required procedures for study withdrawal must be performed on pregnant female subject unless contraindicated by pregnancy (eg, X-ray studies). Other appropriate follow-up procedures should be considered if indicated.

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7.1.3. Laboratory Assessments

The safety laboratory assessments will be performed in accordance to the Schedule of Assessments: Table 1.

Blood samples will be collected using a standard output from the dialysis lines (Figure 2).

The safety laboratory analyses in blood will be performed at the local clinical units in EU and will be performed at a central laboratory in USA, according to their validated methods.

Haematology and Clinical Chemistry

- *Haematology*: Haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, erythrocyte and leucocyte count and differential (absolute and percentage), and platelets
- *Clinical chemistry (serum)*: Creatinine, CK, total protein, albumin, cholesterol, LDL, HDL, triglycerides, glucose, BUN, bilirubin, sodium, potassium, calcium, phosphate, ALP, AST, ALT, and gamma-glutamyl transferase
- *Clinical chemistry (serum)*: magnesium, iron (ferritin and transferrin)
- *Heavy metals (total blood; collected in sodium heparin or EDTA (dark blue))*: zinc
- *Ionised calcium (total blood)*
- Hb1Ac (*total blood*)
- *PTH (plasma, EDTA):* We recommend blood samples for PTH measurement should be taken into tubes containing EDTA, ideally between 10:00 and 16:00, and plasma separated within 24 h of venepuncture. Plasma samples should be stored at 4°C and analysed within 72 h of venepuncture. If plasma is not available, PTH from serum samples is also accepted.

Pregnancy Test

A serum pregnancy test will be performed at Screening, in female patients of childbearing potential, followed by a urine pregnancy test on a monthly basis, should urine be available.

7.1.4. 12-Lead Electrocardiograms

A 12-lead ECG will be obtained with the patient supine or semi-reclined and will be performed in accordance with the Schedule of Assessments (Table 1).

The Investigator will perform an overall evaluation of the ECG strips for safety purposes and the recording will be reported as “normal”, “abnormal not clinically significant (NCS)”, or “abnormal clinically significant (CS)”. Abnormalities

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of clinical significance should be recorded as an AE. Cardiac intervals: PRT axis, PR, QRS, QT, RR, HR, QTcB, and QTcF will be measured.

Electrocardiogram Abnormalities

As QTc prolongation is common in ESRD patients on HD and can occur due to underlying CVC disease, haemodialysis, sodium thiosulfate, calcimimetics, electrolyte disturbances (Ca, Mg and K) and overdoses of SNF472, careful QTc assessment is essential. Any QTc interval using Bazett's formula (QTcB) >500 ms or increase >60 ms from baseline in 1 or more subjects as confirmed with consecutive ECGs will be considered abnormal. It will be reported as an AE if the investigator considers it clinically relevant. Investigators should use their discretion to monitor the subject, apply appropriate management and observe until the QTcB has decreased. At the discretion of the investigator, patients with persistent QTc prolongation may be withdrawn from the trial.

7.1.5. Physical Examinations

The physical examinations will be performed in accordance with the Schedule of Assessments: Table 1.

The physical examination comprises a routine medical examination.

The routine medical examination will be recorded as "normal" or "abnormal".

7.2. Haemodialysis-related Events

The following events are known to occur during dialysis treatments:

- Hypotension
- Muscle cramps
- Disequilibrium syndrome
- Nausea and vomiting
- Headache
- Chest pain
- Itching
- Fever and chills
- Pyrogen reaction
- Hypertension

Occurrence of these events during the dialysis treatment procedure should be recorded in the CRF and indicated as haemodialysis-related events. If any of these events are considered to be unrelated to the hemodialysis treatment procedure, they should be recorded as standard adverse events.

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7.3. Pharmacokinetic and Pharmacodynamic Parameters

7.3.1. Pharmacokinetic and Pharmacodynamic Blood Sample Collection and Handling

Blood samples for PK and PD analyses of SNF472 will be collected according to the Schedule of Assessments (Table 1).

See separate laboratory manual instructions for detailed description of PK and PD sample collection.

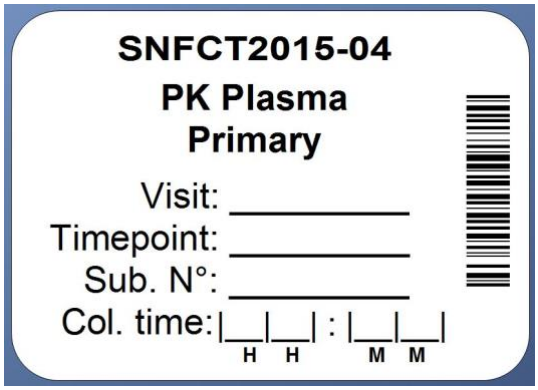
The actual date and time of each blood sample collected will be recorded.

Blood samples will be collected using one of the lines already connected to the patient (Figure 2).

Approximately, 4 mL of blood at pre-dose and 4 mL of blood at end of infusion will be collected into polyethylene terephthalate (Vacutainer) tubes containing potassium (K_3) EDTA. Samples will be divided into aliquots for PK and PD sampling according to the laboratory manual instructions.

Tubes will be labelled with the following minimum information: clinical study number, Patient ID, sample type, day and time, primary or back-up sample (see sample label, Figure 3).

Figure 3 Cryovial sample labels for sample collections



All samples will immediately be placed on crushed ice and centrifuged (1900*g* for 10 minutes at 4°C) within 30 minutes of collection. The resultant plasma for each time-point will be divided into aliquots according to the laboratory manual instructions and transferred into appropriately labelled PET tubes (e.g., 1.8 mL storage cryovials). Plasma samples should be kept on dry ice at the site until courier collection. Samples will be stored at -80ºC.

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Samples for GLP PK analysis will be packed on dry ice and shipped by courier to the [redacted] depot for storage in Europe:

[redacted]

Samples for GLP PK analysis will be packed on dry ice and shipped by courier [redacted]:

[redacted]

[redacted]

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7.3.2. Pharmacokinetic Variables

The following PK parameter will be assessed for SNF472:

C_{max} Maximum observed plasma concentration

7.4. Biomarkers

Blood samples for biomarker (BK) analysis will be collected according to the Schedule of Assessments: Table 1. Biomarkers will be defined and analysed at the end of the study.

The actual date and time of each blood sample collected will be recorded.

The 2 mL blood sample at pre-dose and end of infusion (in duplicate = 4 ml) will be collected into serum-separating gel PET tubes (Vacutainer) to obtain serum (as described in Table 1). All samples will be then centrifuged (1500*g* for 10 minutes). The resultant serum for each time-point (in duplicate) will be divided into 2 aliquots (250 µL serum per aliquot each for Aliquot 1/2 and Aliquot 2/2) and transferred to 2 appropriately labelled PET tubes (e.g., 1.8 mL storage cryovials). Samples stored at -80ºC.

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Serum samples for biomarker analysis will be packed on dry ice and shipped by courier at the end of the study (single shipment) to in Europe:

[redacted]

[redacted]

[redacted]

[redacted]

7.5. Scores and Evaluations

Several different scores and evaluations will be performed throughout the study (see Table 1).

The assessment of the degree of pain a patient feels will be measured with the VAS.

To assess the course of healing of the ulcers, the Bates Jensen Wound Assessment Tool will be used. Of note, elements of the Bates-Jensen Wound Assessment tool which imply probing the wound or measuring its depth are left to the discretion of the treating physician at the site and are not compulsory.

Quality of life will be assessed with the Wound QoL score.

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Images of the primary, secondary, and tertiary wounds will be taken at regular intervals and uploaded into the clinical database.

7.5.1. Pain Score -VAS

The Visual Analogue Scale (VAS) will be used to assess pain, as per the patient. A VAS is a measurement instrument that aims to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. For example, the amount of pain that a patient feels ranges across a continuum from none to an extreme amount of pain.

Operationally, a VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end, as illustrated in

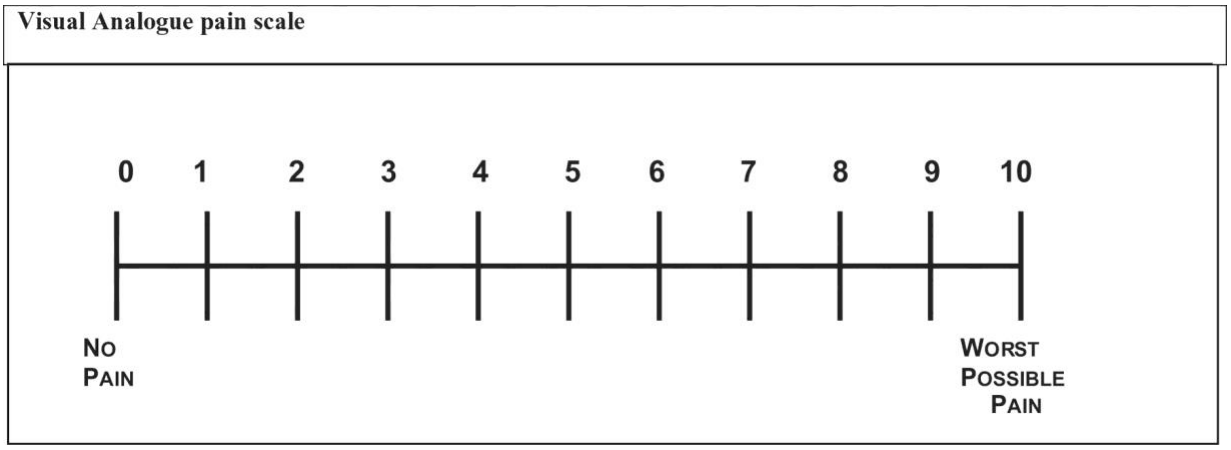

Figure 4The patient marks on the line the point that he feels represents his perception of his current status. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point that the patient marks [51].

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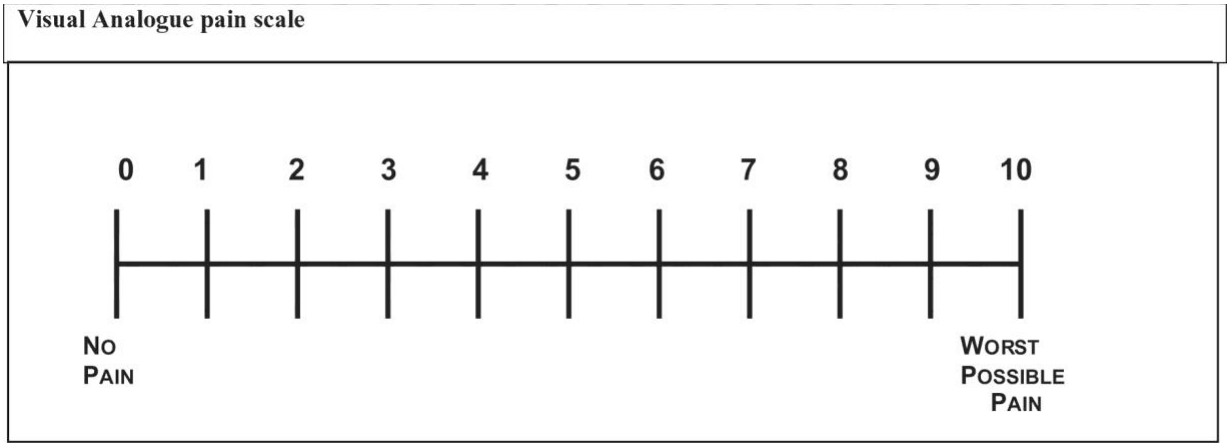

Figure 4: VAS Analogue Scale

7.5.2. Lesion Score – Bates-Jensen Wound Assessment Tool

The site investigator will use the Bates Jensen Wound Assessment Tool (BWAT) to assess the course of the lesion. BWAT is a measuring instrument used to assess and monitor healing in pressure ulcers and other chronic wounds[49]. It is not, however, specific for CUA. It uses a numerical scale to rate wound characteristics from best to worst possible. It consists of 15 items, two of which (location and shape) are not scored. Scored items are:

- Size
- Depth
- Edges
- Undermining or pockets
- Necrotic tissue type
- Necrotic tissue amount
- Exudate type
- Exudate amount
- Surrounding skin colour
- Peripheral tissue oedema
- Peripheral tissue induration
- Granulation tissue
- Epithelialization

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Each item should be scored from 1 to 5, with 1 being the best for that attribute.

Of note, elements of the Bates-Jensen Wound Assessment tool which imply probing the wound or measuring its depth are left to the discretion of the treating physician at the site and are not compulsory. The BJWAT total score will be calculated using a standard methodology for any missing values. Additionally, scores for the component items will be assessed longitudinally. Improvement or worsening will be assessed in the total score and the individual component scores.

7.5.2.1. Image Acquisition Process

Pictures will be taken from the patient's lesions at the visits detailed in the Schedule of Assessments Table 1.

At baseline and for inclusion criterion purposes, as per the site investigator, several pictures of the primary lesion should be taken in order for [redacted] to decide which image is the best quality image, to include in the database, as the primary lesion. Thereafter, all other pictures of the primary lesion should be taken in the same way (light, angle, etc.) as the baseline one so that the course of the wound can be assessed. Color reference cards with an individual barcode (unique patient identifier) which will be recorded into the CRF and optimized for automatic detection and reading should be placed next to the lesion before any image is taken.

Similar rules apply for the secondary and tertiary lesions.

All pictures will be uploaded into the database. The pictures will be linked to their corresponding visit.

7.5.2.2. Image Analyses

Lesion images will be analysed using the following methods.

1. Two reviewers will independently perform a two-step review of the lesion images:

    a. The first step is a patient-level analysis in which the baseline and final images for each patient are de-identified with respect to order and are randomly labeled as image A or image B. Each reviewer will compare the images to assess whether image A is worse, image B is worse, or if there is no difference between images A and B. If there is discordance between the reviewers' assessments, the reviewers will discuss the case together to attempt concordance.

    b. The second step is a review of all patient images taken as baseline and every two weeks during the 12-week trial. Each on-treatment analysis will be compared to baseline and scored as worsened, improved, or no change. The aggregated categorical scores across all patients for each time point will be correlated with the aggregate BWAT total score for each corresponding time point. If there is discordance between the reviewers' assessments, the reviewers will discuss the case together to attempt concordance.

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2. The patient images will be color calibrated and analysed using JMP (a SAS product) to produce an RGB (Red Blue Green) score. The RGB scores will be used to calculate image changes over the course of each patient's study participation.

7.5.3. Quality of Life - Wound QOL (HRQOL)

The Wound-QoL questionnaire measures the disease-specific, health-related quality of life of patients with chronic wounds. It consists of 17 items on impairments which are always assessed in retrospect to the preceding seven days. The Wound-QoL is completed by the patient [52]. The Wound-QoL will be available in the specific language of each participating country for this study (English and Spanish) to ensure that each patient will understand all questions. All the information (questions/answers) will be entered into the CRF. The global score and subscale scores will be calculated programmatically in accordance with the scoring rules. The source data (paper) will be faxed / emailed to the sponsor and the original kept in the Investigator Files (TMF).

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8. STUDY CONDUCT

8.1. Schedule and Time of Assessments

The Schedule of Assessments to be performed for each part of the clinical trial is described in Table 1.

The following priority order will be in effect when more than one assessment is required at a particular time-point, with PK blood sampling being performed nearest to the specified time:

1. Lesion and pain score
2. Blood samples for safety assessments
3. 12 Lead ECG
4. PK and biomarker blood sampling
5. HRQOL score (wound QOL)

8.2. Assessments by Visit

The Schedule of Assessments to be performed for each part of the clinical trial can be found in Table 1.

8.2.1. Screening Period W-2 to Day-1 (hence the screening/recruitment period is up to 2 weeks)

Potential patients for the inclusion in the clinical trial will be informed about the study and asked to attend the Screening Visit within 14 days before receiving the first dose of IMP. The Investigator has to confirm that patients are on standard of care as per the site's SOPs. Written informed consent will be obtained from all patients before any screening procedures are performed. Patients will be fully informed of their responsibilities, of all the procedures expected to be performed in the clinical trial, the possible risks, disadvantages and potential benefits of being dosed with SNF472 and their rights while participating in the clinical trial. They will have the opportunity to ask questions and have time to consider participation. If the patient wishes to participate in the clinical trial, they will be asked to sign and date the ICF.

The Screening Visit will be carried out and a 12-Lead ECG, will be taken, demographic, including body weight (dry weight) and anthropometric data, physical examination, medical history and treatment history (prior medication) data. Safety laboratory assessments (including clinical chemistry, haematology and a serum pregnancy test) will be taken from the routine safety laboratory analysis whenever possible.

The patient will be asked to draw the level of pain experienced on the VAS.

Patients will be considered eligible to participate in the clinical trial if they successfully complete the Screening Visit, meet all the inclusion criteria, and the lesion is considered to fulfil CUA requirements, as per [redacted].

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Patients can start treatment at any point in time during the initial 2-week period at the PI's discretion or if the PI decides that the patient is not adequately responding to the SOC.

8.2.2. Expected Duration of the Clinical trial

The maximum expected duration for an individual patient of the clinical trial, including Screening and Follow-up, will be approximately 15 weeks.

8.2.3. Treatment Period W1-W12

All eligible patients will receive SNF472 during their haemodialysis sessions. SNF472 will be administered at each dialysis session for the entire duration of the study. The duration of infusion of SNF472 will range from 2.5 h up to maximum time on dialysis, which would be 4 h. SNF472 should NOT be administered directly intravenously. SNF472 should NOT be administered concomitantly with STS, should STS be used. In case both drugs would be administered to the patient, the administration of SNF472 should be stopped 30 minutes before the end of the dialysis session to allow the STS infusion to take place in the last 30 minutes of the session.

In the event of Fe+ administration, the infusion of SNF472 should be stopped BEFORE starting the Fe+ infusion.

For other assessments please check Table 1.

8.2.4. Follow-Up Visit W13

All patients will undergo a physical examination, a 12-lead ECG, and be assessed for resolution of pending AEs and SAEs. In addition, safety laboratory assessments will be performed and the pain and lesion scores will be assessed.

8.2.5. End of Study Visit

Patients who withdraw consent or are withdrawn from the clinical trial should, if possible, have an End of Study Visit. This visit should take place as soon as possible after the patient has withdrawn consent or has withdrawn from the clinical trial. The assessments and procedures scheduled for the Follow-Up Visit should be performed at the End of Study Visit.

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8.3. Restrictions

8.3.1. Contraception Requirements

The use of highly effective contraception methods to prevent pregnancy, of a female participant or a female partner of a male participant, from the day of dosing and for 3 months after the follow-up visit, is necessary.

- Male patients:
    - Male patient who have not had a vasectomy and have a female partner of childbearing potential, must use a condom with spermicide when having heterosexual intercourse, from the time the consent form is signed until 3 months after the last dose of study drug
    - If the male patient's partner is of childbearing potential or if she has had a tubal ligation without having had her ovaries taken out and she is taking a hormonal contraceptive, she may choose to continue taking the hormonal contraceptive but it is strongly recommended to add 1 non-hormonal method of contraception (i.e., male condom with spermicide, female condom, diaphragm with spermicidal jelly or a cervical cap). We strongly recommend the partner, must use reliable forms of contraception during the study and for 3 months after the last dose of study drug
- Highly effective contraceptive methods are:
    - Combined (estrogen and progesterone containing) oral, intravaginal or transdermal contraceptive associated with inhibition of ovulation + condom with spermicide
    - Progesteron-only oral, injectable or implantable hormonal contraception associated with inhibition of ovulation + condom with spermicide
    - Intra uterine device (IUD) + condom with spermicide
    - True abstinence: When this is in line with the patient´s preferred and usual lifestyle. Periodic abstinence (e.g., calendar, ovulation, symptothermal (monitoring of your body temperature), post-ovulation methods), and withdrawal are NOT acceptable methods of contraception.
    - Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- Female patients must be in one of the cases described below:
    - Absence of menstruation for 12 consecutive months (menopause) and the doctor confirms they are postmenopausal
    - Both ovaries and uterus have been removed by surgery
    - Cannot get pregnant due to having ovarian problems (confirmed by a doctor)
    - If of childbearing potential, the female patient and their partner have to use highly effective forms of contraception (see above) during the study and for 3 months after the last dose of study drug

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9. STATISTICAL METHODS

All statistical analyses and programming of tables, figures, and listings will be performed by [redacted] using the latest available version of SAS® (SAS Institute Inc., Cary, North Carolina, USA).

Before database lock, a Statistical Analysis Plan (SAP) will be issued as a separate document, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses as mentioned in detail in the SAP will be described and justified in the final integrated Clinical Study Report.

9.1. Clinical Trial Population

9.1.1. Disposition of Patients

Disposition data will be listed and summarised overall. A listing of withdrawals will also be presented including the primary reason for withdrawal.

9.1.2. Protocol Deviations

Deviations from the Clinical Trial Protocol, including deviations of inclusion/exclusion criteria will be assessed as "minor" or "major" in agreement with the Sponsor, prior to database lock.

9.1.3. Analysis Populations

Safety population:	All patients who receive at least 1 dose of IMP will be included in the safety population.
Efficacy Population:	All patients who receive at least 75% of SNF472 doses and for whom at least baseline and Week 12/EOS images are readable will be part of the Efficacy Population.

9.2. General Considerations

All efficacy (ulcer size, Bates-Jensen Wound tool assessments, pain scale, and wound QoL), PK and safety parameters as well as population characteristics will be listed and described using summary statistics. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated for each quantitative variable (unless otherwise stated). Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable.

All listings will be sorted by patient number, time-point, and parameter (if applicable).

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9.3. Demographic and Anthropometric Information, Baseline Characteristics, and Concomitant Medications

Demographic data will be listed and summarised.

Medical history data will be listed and summarised.

Prior medications are defined as those taken until the time of the first IMP administration. Concomitant medications are defined as those taken at the time of or after the first IMP administration.

Prior and concomitant medication will be coded according to the latest available version of the World Health Organisation's Drug Dictionary (WHO-DD) and the Anatomical Therapeutic Chemical classification system. Prior and concomitant medication will be listed separately.

9.4. Pharmacokinetic Analysis

The plasma SNF472 PK parameter, Cmax, will be calculated, individual and mean.

9.5. Determination of Sample Size

Based on recent historical data from a U.S. large dialysis provider organization, approximately 25% of calciphylaxis skin lesions are considered to be improved over a 3-6 month period (data unpublished; personal communication). A total of 15 subjects who complete 12-week of treatment was determined necessary to show with 80% power that the percentage of subjects for which the primary ulcer is totally or partially healed after 12 weeks of treatment is greater than 25%. For these calculations, it was assumed that the percentage of totally or partially healed subjects for SNF472 will be 60%.

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10. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

10.1. Data Quality Assurance

The Sponsor or designee will conduct Clinical Unit visits to, inspect the facilities, and to ensure that all the clinical study procedures are followed as per protocol.

The Investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the clinical trial for each clinical trial patient. All information recorded in the CRF for this clinical trial must be consistent with the patient's source documentation.

10.2. Data Collection

Paper CRFs will be distributed to the clinical sites. Once the CRFs are source data verified, the originals are sent to the sponsor. The sponsor digitizes the CRFs for data entry. The data from the digitized CRFs will be entered into a database using [redacted]

Once the original CRFs are sent to the sponsor, all data additions, changes or corrections will be captured on the query reports.

The responsible Clinical Monitor will check source data during the monitoring visits to the Clinical Unit. The Investigator will ensure that the data collected are accurate, complete and legible.

All clinical work conducted under this Clinical trial Protocol will follow Good Clinical Practice (GCP) principles [54].

10.3. Source Documents

All data obtained during the clinical trial should be promptly recorded in the CRF, as is described in section 10.2.

The CRF entries for each patient will be checked against source documents by the monitor. Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

10.4. Access to Source Documents

During the course of the clinical trial, a Monitor will make Clinical Unit visits to review Clinical Trial Protocol compliance, assess IMP accountability and ensure that the clinical trial is being conducted according to pertinent regulatory requirements. CRF entries will be verified against source documents. The review of medical records will be handled confidentially to ensure clinical trial patient anonymity.

Checking of CRF entries for completeness and clarity and verifying with source documents, will be required to monitor the clinical trial for compliance with GCP and other regulations. Moreover, Regulatory Authorities of certain countries and ECs/IRBs may wish to carry out source data inspections on-site, and the Sponsor's Clinical Quality Assurance

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Group may wish to carry out audits. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and patient confidentiality. The Investigator assures the Sponsor of the necessary support at all times.

10.5. Data Management

[redacted]

A data management plan (DMP) will describe the work- and data-flow within this clinical trial. Versions for the computer systems and the coding will be defined in the DMP.

10.6. Archiving Clinical Trial Documents

According to International Conference on Harmonisation (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. However, these documents should be retained for a longer period if required by the applicable legal requirements.

10.7. Good Clinical Practice

The procedures set out in this Clinical trial Protocol are designed to ensure that the Sponsor and the Investigator abide by the principles of the ICH guidelines on GCP[54], and the Declaration of Helsinki (Version 1996)[55]. The clinical trial will also be carried out in keeping with national and local legal requirements.

10.8. Informed Consent

Before each patient is enrolled in the clinical trial, written informed consent will be obtained from the patient according to the local regulatory and legal requirements. The Patient Information Sheet and ICF must be signed and dated; one copy will be handed to the patient and the Investigator will retain a copy as part of the clinical trial records. The Investigator will not undertake any investigation specifically required for the clinical trial until written consent has been obtained. The terms of the consent and when it was obtained must also be documented in the CRF.

The Investigator must ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the clinical trial. Patients must also be notified that they are free to withdraw from the clinical trial at any time without prejudice to future care. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

If a Clinical Trial Protocol Amendment is required, the Patient Information Sheet and ICF may need to be revised to reflect the changes to the Clinical Trial Protocol. If the Patient Information Sheet and ICF are revised, they must be

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reviewed and approved by the responsible EC/IRB, and signed by all patients subsequently enrolled in the clinical trial as well as those currently enrolled in the clinical trial.

10.9. Protocol Approval and Amendment(s)

Before the start of the clinical trial, the Clinical Trial Protocol and other relevant documents will be approved by the EC/IRB/Regulatory Authorities in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the clinical trial.

This Clinical Trial Protocol should be followed exactly. To alter the Clinical Trial Protocol, amendments must be written, which must be released by the responsible staff and receive EC/IRB/Regulatory Authority approval prior to implementation (as appropriate).

Administrative changes may be made without the need for a substantial Clinical Trial Protocol Amendment, but will also be mentioned in the integrated Clinical Study Report. All Clinical Trial Protocol Amendments will be distributed to all Clinical Trial Protocol recipients, with appropriate instructions.

10.10. Duration of the Clinical trial

The maximum expected duration of participation for an individual patient, including Screening and Follow-up, will be approximately 15 weeks.

10.11. Confidentiality Data Protection

All clinical trial findings and documents will be regarded as confidential. The Investigator and members of his research team must not disclose such information without prior written approval from the Sponsor. The Investigator shall permit access to subject's records and source documents for the purpose of monitoring, auditing or inspection by Sanifit, authorized representatives of Sanifit, regulatory authorities and IRB/IEC's only.

The anonymity of participating patients must be maintained. Patients will be specified on documents by their patient number, initial or birth date, not by name. Documents that identify the patient (e.g., the signed Patient Information Sheet and ICF) must be maintained in confidence by the Investigator.

10.12. Other Ethical and Regulatory Issues

If a safety issue of clinical relevance is identified, from review of any data, then the Sponsor will issue prompt notification to all parties – Investigator and EC/IRB/Regulatory Authorities.

A safety issue of clinical relevance is one that has a relevant impact on the course of the clinical trial or program (including the potential for suspension of the clinical trial program or amendments to the Clinical Trial Protocol) or warrants immediate update of the Patient Information Sheet and ICF.

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10.13. Liability and Insurance

The Sponsor will take out reasonable third party liability insurance cover in accordance with all participating countries (Spain, UK, and USA) legal requirements. The civil liability of the Investigator, the persons instructed by him and the hospital, practice or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this clinical trial are governed by the applicable laws and GCP guidelines.

The Sponsor will arrange for patients participating in this clinical trial to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the clinical trial.

The method and manner of compensation to patients should comply with applicable regulatory requirement(s).

[redacted]

10.14. Publication Policy

The sponsor recognizes the fundamental obligation of the institution for publication of nature, purpose and result of the work performed.

With regard to a publication about the substance SNF472 the Institution, upon Sponsor's previous written consent, shall have the right to publish or present the results of the Study conducted under this Agreement, including Study Data after providing a copy of the proposed publication to the Sponsor at least thirty (30) days prior to submission for publication or disclosure and at least ten (10) days prior to submission for Abstracts. If the Sponsor believes that the manuscript contains any of its Confidential Information or subject matter that is patentable or otherwise protected by IP rights, the sponsor can exceptionally demand a delay of the publication to maximum 90 days after submission of the manuscript, if this is necessary for the protection of intellectual property. The notification will include specific details to be amended from the manuscript in mutual understanding. The approval shall not be unreasonably denied and the scientific content may not be changed. If no objection is received in writing within the above mentioned period, the Party seeking disclosure will be free to publish the manuscript or other form of disclosure as submitted to the Sponsor.

[redacted] The Sponsor retains the right to nominate authors in any publication at its sole discretion, provided they contributed in the conception, design, execution, follow-up and/or discussion of results of the study.

The Institution shall grant, and shall cause the Coordinating Investigator and the German Principle Investigators to grant, the Sponsor a worldwide, royalty-free, non-exclusive license to reproduce and distribute copies of any Publication relating to the Study in which the Institution, the Principal Investigator, or any other Study Staff member retains the

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copyright. The Institution will publicly acknowledge in each Publication the Sponsor's contribution as follows: "Data used in preparation of this manuscript were obtained with support of Laboratoris Sanifit (plus Address)".

The institution can publish all data which are collected regardless of the substance SNF472 (for example, but not finally: Calciphylaxis Foreground, Imaging systems or methods etc.) without prior submission and approval by the sponsor.

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11. REFERENCE LIST

1. http://www.accessdata.fda.gov/scripts/fdcc/?set=SCOGS.
2. Davies, N.T. and S.E. Olpin, *Studies on the phytate: zinc molar contents in diets as a determinant of Zn availability to young rats.* Br J Nutr, 1979. **41**(3): p. 590-603.
3. Forbes, R.M., H.M. Parker, and J.W. Erdman, Jr., *Effects of dietary phytate, calcium and magnesium levels on zinc bioavailability to rats.* J Nutr, 1984. **114**(8): p. 1421-5.
4. Pallauf, J., et al., *Supplemental sodium phytate and microbial phytase influence iron availability in growing rats.* J Trace Elem Med Biol, 1999. **13**(3): p. 134-40.
5. March, J.G., B.M. Simonet, and F. Grases, *Determination of phytic acid by gas chromatography-mass spectroscopy: application to biological samples.* J Chromatogr B Biomed Sci Appl, 2001. **757**(2): p. 247-55.
6. March JG, S.B., Grases F, Salvador A., *Indirect determination of phytic acid in urine.* Anal. Chim. Acta, 1998. **367**: p. 63-68.
7. Grases F, P.J., Isern B, Prieto RM., *Determination of myo-inositol hexakisphosphate (phytate) in urine by inductively coupled plasma atomic emission spectrometry (ICP-AES).* Anal. Chim. Acta., 2004. **510**: p. 41-43.
8. Perelló J, I.B., Muñoz JA, Valiente M, Grases F., *Determination of phytate in urine by high performance liquid chromatography – mass spectrometry.* Chromat., 2004. **60**: p. 265-268.
9. Grases F, L.A., *Determination of phytic acid in urine by ICP atomic emission spectrometry.* Anal. Lett., 1996. **29**: p. 1193-9.
10. Grases, F., et al., *Urinary phytate in calcium oxalate stone formers and healthy people--dietary effects on phytate excretion.* Scand J Urol Nephrol, 2000. **34**(3): p. 162-4.
11. Curhan, G.C., et al., *Dietary factors and the risk of incident kidney stones in younger women: Nurses' Health Study II.* Arch Intern Med, 2004. **164**(8): p. 885-91.
12. Conte, A., et al., *Urinary lithogen risk test: usefulness in the evaluation of renal lithiasis treatment using crystallization inhibitors (citrate and phytate).* Arch Esp Urol, 1999. **52**(3): p. 305-10.
13. Grases, F., et al., *Effect of tetracalcium dimagnesium phytate on bone characteristics in ovariectomized rats.* J Med Food, 2010. **13**(6): p. 1301-6.
14. Lopez-Gonzalez, A.A., et al., *Phytate (myo-inositol hexaphosphate) and risk factors for osteoporosis.* J Med Food, 2008. **11**(4): p. 747-52.
15. Lopez-Gonzalez, A.A., et al., *Phytate levels and bone parameters: a retrospective pilot clinical trial.* Front Biosci (Elite Ed), 2010. **2**: p. 1093-8.
16. Grases, F., et al., *Phytate (Myo-inositol hexakisphosphate) inhibits cardiovascular calcifications in rats.* Front Biosci, 2006. **11**: p. 136-42.
17. Grases, F., et al., *Effect of crystallization inhibitors on vascular calcifications induced by vitamin D: a pilot study in Sprague-Dawley rats.* Circ J, 2007. **71**(7): p. 1152-6.
18. Van den Berg CJ, H.L., Stanbury SW. , *Inositol phosphates and phytic acid as inhibitors of biological calcification in the rat.* Clin. Sci., 1972. **43**: p. 377-383.
19. Midorikawa, K., et al., *Protective effect of phytic acid on oxidative DNA damage with reference to cancer chemoprevention.* Biochem Biophys Res Commun, 2001. **288**(3): p. 552-7.
20. Reddy, B.S., *Prevention of colon carcinogenesis by components of dietary fiber.* Anticancer Res, 1999. **19**(5A): p. 3681-3.
21. Graf, E. and J.W. Eaton, *Dietary suppression of colonic cancer. Fiber or phytate?* Cancer, 1985. **56**(4): p. 717-8.
22. Shamsuddin, A.M., I. Vucenik, and K.E. Cole, *IP6: a novel anti-cancer agent.* Life Sci, 1997. **61**(4): p. 343-54.
23. Gupta, K.P., J. Singh, and R. Bharathi, *Suppression of DMBA-induced mouse skin tumor development by inositol hexaphosphate and its mode of action.* Nutr Cancer, 2003. **46**(1): p. 66-72.
24. Grases F, S.C., Simonet BM, Costa-Bauzá., *Sialolithiasis: mechanism of calculi formation and etiologic factors.* A. Clin. Chim. Acta., 2003. **334**(1-2): p. 131-6.
25. Grases, F., et al., *Anticalculus effect of a triclosan mouthwash containing phytate: a double-blind, randomized, three-period crossover trial.* J Periodontal Res, 2009. **44**(5): p. 616-21.

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26. *Investigator's Brochure for SNF472*, 2012.
27. Grau A, F.-P.C., Grases F, Sanchis P, Perelló J, Isern B, Costa-Bauzá A, Vidal L, Moranta E, Aceña M, Caldés O, Bonnin O, García-Raja A, Bethencourt A., *Relación entre el fitato y calcificaciones valvulares cardíacas. Estudio de campo para diseño de un ensayo clínico en la estenosis aórtica*, in *IV Congreso de la Sociedad Balear de Cardiología*2005: Palma de Mallorca (Mallorca).
28. Addison, W.N. and M.D. McKee, *Inositol hexakisphosphate inhibits mineralization of MC3T3-E1 osteoblast cultures.* Bone, 2010. **46**(4): p. 1100-7.
29. Arriero MdM, R.J., Perelló J, Monjo M. , *Differential response of MC3T3-E1 and human mesenchymal stem cells to inositol hexakisphosphate.* Cell Physiol. Biochem., In press.
30. Lopez-Gonzalez, A.A., et al., *Protective effect of myo-inositol hexaphosphate (phytate) on bone mass loss in postmenopausal women.* Eur J Nutr, 2013. **52**(2): p. 717-26.
31. *Fyton-Summary of Product Characteristics*, IZOtop, Editor 2002.
32. http://www.usrds.org/2015/view/v2_01.aspx. 2015.
33. Noordzij, M., et al., *Renal replacement therapy in Europe: a summary of the 2011 ERA-EDTA Registry Annual Report.* Clin Kidney J, 2014. **7**(2): p. 227-38.
34. Lameire, N., et al., *Chronic kidney disease: a European perspective.* Kidney Int Suppl, 2005(99): p. S30-8.
35. JR, N. *Calciphylaxis - http://www.emedicine.com/derm/byname/calciphylaxis*.
36. Schlieper, G., et al., *Sodium thiosulfate in the treatment of calcific uremic arteriolopathy.* Nat Rev Nephrol, 2009. **5**(9): p. 539-43.
37. Nigwekar, S.U., et al., *Calciphylaxis from nonuremic causes: a systematic review.* Clin J Am Soc Nephrol, 2008. **3**(4): p. 1139-43.
38. Mazhar, A.R., et al., *Risk factors and mortality associated with calciphylaxis in end-stage renal disease.* Kidney Int, 2001. **60**(1): p. 324-32.
39. Brandenburg, V.M., et al., *Calcific uraemic arteriolopathy: a rare disease with a potentially high impact on chronic kidney disease-mineral and bone disorder.* Pediatr Nephrol, 2014. **29**(12): p. 2289-98.
40. Brandenburg, V.M., M. Cozzolino, and S. Mazzaferro, *Calcific uremic arteriolopathy: a call for action.* Semin Nephrol, 2014. **34**(6): p. 641-7.
41. Nigwekar, S.U., et al., *Calciphylaxis: risk factors, diagnosis, and treatment.* Am J Kidney Dis, 2015. **66**(1): p. 133-46.
42. Goel, S.e.a., *Treatment of severe metastatic calcification and calciphylaxis in dialysis patients.* Int J Nephrol, 2011(Feb 24).
43. *IP6Na6: Effect on HERG Tail Currents recorded from Stably Transfected HEK 293 cells*, 2010, b-Sys.
44. Moorthi, R.N. and S.M. Moe, *CKD-mineral and bone disorder: core curriculum 2011.* Am J Kidney Dis, 2011. **58**(6): p. 1022-36.
45. *Evaluation on the effects of an IP6 diet in the treatment of rat dystrophic calcification in soft tissues*, 2004, Universitat de les Illes Balears.
46. Grases, F., et al., *Dietary myo-inositol hexaphosphate prevents dystrophic calcifications in soft tissues: a pilot study in Wistar rats.* Life Sci, 2004. **75**(1): p. 11-9.
47. Perelló J, S.C., Joubert PH, et al. *First-time-in-human phase 1 clinical trial in healthy volunteers with SNF472, a novel inhibitor of vascular calcification*. 2015.
48. Hayashi, M., *Calciphylaxis: diagnosis and clinical features.* Clin Exp Nephrol, 2013. **17**(4): p. 498-503.
49. B, S.C.a.B.-J., *Wound care: a collaborative practice manual for health professionals*, 2011, Lippincott Williams and Wilkins p. 144-154.
50. *K2 Hemodialysis Machine Operator's Manual Rev. H*2008-2014: Fresenius USA Inc.
51. Gould, D., et al., *Examining the validity of pressure ulcer risk assessment scales: developing and using illustrated patient simulations to collect the data.* J Clin Nurs, 2001. **10**(5): p. 697-706.
52. Augustin M, B.K., Herberger K, Protz K, Goepel L, Wild T, Blome C, *Use of the WoundQoL instrument in routine practice: Feasibiliy, validity and development of an implementation tool.* Wound Medicine, 2014. **5**: p. 4-8.

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53. Deserno, T.M., et al., *Integrated image data and medical record management for rare disease registries. A general framework and its instantiation to the German Calciphylaxis Registry.* J Digit Imaging, 2014. **27**(6): p. 702-13.
54. *Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)*, T.E.A.f.t.E.o.M. Products, Editor 2002. p. 1-59.
55. *Declaration of Helsinki. Recommendations Guiding Physicians in Biomedical Research involving Human Patients*, W.M.A. (WMA), Editor Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996.

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