CLINICAL STUDY REPORT

A Prospective Multicenter Phase 2/3 Clinical Trial with Sodium Thiosulfate for the Treatment of Calciphylaxis

Protocol Number: STS-CSM-1/13

SECTION 16

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16.1 *Study Information*

16.1.1 Protocol and protocol amendments

The following documents are included in this section:

- Protocol Version, FINAL 4.3, dated 29-May-2017
- Protocol Version, FINAL 4.2, dated 02 Feb-2017
- Protocol Version, FINAL 3.0, dated 23-Jun-2015

The signatures pages of each protocol version are added at the end of each version.

A Prospective Multicenter Phase 2/3 Clinical Trial with Sodium Thiosulfate for the Treatment of Calciphylaxis

PROTOCOL Nr. STS-CSM-1/13

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Sponsor:

Dr. F. Köhler Chemie GmbH

Dr. Gernot Köhler
Werner-von-Siemens-Str. 14 - 28
D-64625 Bensheim
Germany
Phone: +49-6251-1083-0
Fax: +49-6251-1083-146

Statistician:

Dr. Anton Klingler
Chief Executive Officer
Assign Data Management and Biostatistics GmbH
Stadlweg 23
6020 Innsbruck
Austria
Ph: +43 512 890 064 121
Fax: +43 512 281 514

Monitoring:

Celerion Clinical Research GmbH
Hainburger Strasse 33
1030 Vienna
Austria
Phone: +43 1 40 33 805 0
Fax: +43 1 403 38 05 66

SYNOPSIS

Title	**A prospective multicenter Phase 2/3 study with sodium thiosulfate for the treatment of calciphylaxis**
Study Rationale	Up to now, no prospective clinical trial with STS has been performed. Reasons are that calciphylaxis is a rare condition and treatment is not focused on certain centres. The previous case reports on successful treatments of calciphylaxis patients with STS support the intention to demonstrate the efficacy and safety of STS in this patient population under the conditions of a prospectively planned clinical trial.
Clinical Phase	2/3
Indication	Treatment of calciphylaxis
Objectives	- The objective of this project is to study the potentially beneficial effects of sodium thiosulfate (STS) on the course and outcome of calciphylaxis. - A run-in phase of 2 to 4 weeks will be established, during which patients will be treated with conventional medications and measures. If the investigator observes typical symptoms of calciphylaxis (pain, appearance of more than one wound lesion) and decides that the patient is eligible for the treatment with STS and participation in the clinical trial, a biopsy will be taken to confirm the diagnosis of calciphylaxis by excluding other causes of skin necroses and ulcerations. If a biopsy report of a consisting wound is available at Screening (VR) and the diagnosis of calciphylaxis is confirmed or other causes for necroses and ulcerations were excluded, an additional biopsy is not required. - Patients with rapidly progressive disease under BSC will be allocated to Group A while patients with less progressive or initially stable disease will be allocated to Group B. Patients of both groups will be treated with STS. Both patients groups will be analysed separately, with the former to establish efficacy and the latter to be assessed descriptively. It is expected, that by far the majority of patients will be in the progressor group. - The run-in phase will end on the same day, when patients will start treatment with STS (baseline, V0). - Follow-up visits will be performed after 4 (V1) 8 (V2), 16 (V3), 24 (V4), 36 (V5) and 48 weeks (V6) after start of STS treatment. **Primary Endpoint:** Percent reduction of the total wound area after 24 weeks (V4) compared to baseline (V0) as assessed by 2 independent, blinded dermatologists using a serial photo documentation. The mean

	value of both assessments will be taken. **Secondary Endpoints**: Status of skin lesions: - Total wound area at 8, 16, 36, 48 weeks compared to baseline (V0). - Complete remission of wound area. - Qualitative improvement of skin lesions at 8, 16, 24, 36, 48 weeks as assessed by the revised Photographic Wound Assessment Tool (revPWAT) score and evaluation of a serial photo documentation through 2 independent, blinded dermatologists. - Use of wound debridement Pain: - Reduction of pain in the areas of calciphylaxis after 4, 8, 16, 24, 36 and 48 weeks after start of STS treatment will be compared to baseline (V0) and assessed by a visual analogue scale (VAS) for pain (0-10). This will be done directly before changing the wound dressing. - Consumption of pain medication (normalized to morphine equivalent with an appropriate conversion table) will be assessed at VR, V0 and 4, 8, 16, 24, 36 and 48 weeks after start of STS treatment and compared to baseline (V0). Clinical global impression: - Change in clinical global impression as assessed by the Clinical Global Impressions-Improvement (CGI-I) score at each follow-up visit (after 4, 8, 16, 24, 36 and 48 weeks) compared to baseline (V0) and the Clinical Global Impression-Severity scale (CGI-S) through the investigators. The Clinical Global Impression-Severity scale (CGI-S) will be assessed at each visit from visit V0 to V6 (i.e. after 4, 8, 16, 24, 36 and 48 weeks). Improvement leading to eligibility of the patient for kidney transplantation - Eligibility for kidney transplantation is given when the patient is being actively listed on a transplant waiting list. Occurrence of new lesions: - Time point of occurrence and – if applicable – healing as well as location of each lesion to be documented at each visit (V0 to V6) Bone mineral density (BMD)

	- Bone scans by Dual Energy X-ray absorptiometry (DEXA) technique at baseline and after 48 weeks (V6) Survival: - Median overall survival after start of STS treatment - One-year survival rate **Safety parameters:** - Adverse events - Adverse events of special interest (AESI; incidence of infections and sepsis, metabolic acidosis, ventricular tachycardia, hypotension, bone fractures). - Use of other concomitant medications - Physical examinations, ECGs, vital signs (heart rate, blood pressure) - Tolerability of STS treatment Laboratory parameters (PTH, total calcium, phosphorus, alkaline phosphatase, pH, CRP, leucocytes, hemoglobin, creatinine, albumin), **Biobanking:** - collection of serum for assessing further relevant parameters, e.g. inflammatory and calcification parameters and bone turn-over markers - T50 test (in vitro blood test for calcification propensity by monitoring the maturation time (T50) of calciprotein particles in serum.
Study design	The study design is a prospective, open, uncontrolled multicenter, Phase 2/3 clinical trial including various dialysis centers in Europe Each patient will serve as his/her own control. A median reduction of at least 50% in total wound area at V4 compared to V0 is expected for patients treated with STS. This is far above the 20% wound reduction which is already considered as clinically relevant. Patients with suspected calciphylaxis will be asked if they agree to participate in the clinical trial and to undergo STS treatment, after conventional medications and measures given during the run-in phase of 2 to 4 weeks were assessed by the investigator as insufficiently or not at all effective. The study duration for each patient will be up to 48 weeks after start of STS treatment. Patients, who will need further treatment after the end of this

	clinical trial, will be treated according to current BSC at the respective study site. At 0.5 and 1 year after the end of the clinical trial, the investigators will be contacted again and asked about the disease status, continuation of STS treatment and survival of the patients, further/additional treatment and new medication for treatment of calciphylaxis.
Number of Subjects	The study population will consist of 40 dialysis patients diagnosed with calciphylaxis.
Duration of Study	The duration of participation for each patient will be up to 48 weeks plus 2 to 4 weeks run-in phase. The overall duration of the trial is expected to be approximately 4 years.
Inclusion Criteria	(1) All patients ≥ 18 years (2) Male or female hemodialysis (HD) patients with a diagnosis of calciphylaxis. (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching). (3) Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study
Exclusion Criteria	(1) (1) Females who are pregnant (positive pregnancy test at screening or during study phase) or lactating. If having reproductive potential are considered potentially ineligible with respect to use highly effective methods of birth control throughout the study. (2) Patients who have participated in any other investigational studies within 30 days previous to enrollment (3) History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment. (4) Good response to conventional treatment. (5) Life expectancy less than 4 months in the judgment of the investigator
Treatments	At start of the run-in phase (VR) of 2 to 4 weeks, patients will be treated with conventional medications and measures. If the investigators assess the patients as eligible for the treatment with STS and for participating in the clinical trial, a biopsy will be taken during the run-in phase to confirm the diagnosis of calciphylaxis by excluding other causes of necroses and ulcerations.

	At the end of the run-in phase, i.e. the day defined as baseline (V0), patients will be treated with STS for at least 24 weeks. The starting dose will be 25 g per day given 3x per week 30 min before end of HD over an infusion period of 60 min. In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms. In case of complete remission of the wound lesion after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4) the dose may only be reduced for safety reasons. Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed.
Safety Parameters	Safety assessments start at the time point, when the patient enters the run-in phase (VR). If the patient is excluded from the trial at baseline (V0) because the diagnosis of calciphylaxis cannot be confirmed, other eligibility criteria are not met or because the patient withdraws the consent for STS treatment, the patient will not be followed up in the trial beyond that time point for further assessments of safety parameters.
Sample Size Determination	Based on published data, a very strong effect on the primary efficacy variable with a standardized effect size (Cohen‘s d) of at least 0.6 is expected, corresponding e.g. to a median reduction in wound area of 60% with a standard deviation of 100%. A sample size of 25 patients will have 80% power to detect a significant result with a 0.025 one-sided significance level under these assumptions. Given a possibly high drop-out rate and also some non-progressing patients which will not be assigned to the efficacy analysis group, a total number of 40 patients will be recruited.
Statistical Analysis	The main statistical analysis of the primary and secondary efficacy parameters will be performed on the FAS using a pattern mixture model approach for missing data. As there will be no control group, optimistic assumptions about disease development for untreated patients will be used for the efficacy analysis. The primary efficacy variable percent reduction in the total wound

	area until V (24 weeks) will be analyzed with a One-sample Wilcoxon signed rank test.

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ALAT	Alanine Transferase
AP	Alkaline Phosphatase
ASAT	Aspartate Transferase
BSC	Best Supportive Care
CGI-I	Clinical Global Impressions-Improvement score
CGI-S	Clinical Global Impression-Severity scale
CKD	Chronic Kidney Disease
CRP	C-reactive protein
CTx	turn-over marker for bone resorption
CUA	Calcific Uremic Arteriolopathy
COMP	Committee of Orphan Medicinal Products
EC	Ethics Committee
eCRF	electronic Case Report Form
EMA	European Medicines Agency
ESRD	End Stage Renal Disease
ETHE1	Ethylmalonic Encephalopathy 1
FAS	Full Analysis Set
FFP	Fresh Frozen Plasma
GGT	Gamma-glutamyltransferase
HD	Hemodialysis
LOCF	Last Observation Carried Forward

MGP	Matrix GLA protein
pO_2	Oxygen Partial Pressure
PPS	Per-Protocol Set
PSUR	Periodic Safety Update Report
PTH	Parathyroid Hormone
pVO_2	Venous Oxygen Tension
SAP	Statistical Analysis Plan
SB	Standard Bicarbonate
SFU	Survival Follow Up
sO_2	Venous Oxygen Saturation of Hemoglobin
SQR	Sulfur-Quinone Oxidoreductase
STS	Sodium Thiosulfate
TS	Thiosulfate
TST	Thiosulfate Sulfurtransferase (= Rhodanese)
VAS	Visual Analogue Scale

1 INTRODUCTION AND BACKGROUND

1.1 Information on Calciphylaxis

Calciphylaxis, also known as calcific uremic arteriolopathy (CUA), is a rare but catastrophic disease which mainly affects patients with end stage renal disease (ESRD) and is associated with a 1-year mortality of 60-80% of the patients (Wilmer and Magro, 2002; Weenig, 2008; Schlieper et al., 2009; Rogers and Coates, 2010). Calciphylaxis is histologically characterized by the triad of calcification of the media, proliferation of the intima, and thrombosis of the lumen of small skin vessels. Clinically, these changes lead to progressive and very painful non-healing ischemic skin ulcerations typically at the lower extremities and/or the abdomen. Assuming an annual incidence of 1-2% among dialysis patients (Musso et al., 2009), (Fine and Zacharias, 2002), (Angelis et al., 1997), e.g. in Switzerland, an estimated 15 to 25 new cases of calciphylaxis are currently expected to occur per year.

Unfortunately, to date there are neither proven therapies available for calciphylaxis, nor is there an established animal model to study its pathophysiology and to test potential treatment modalities. Clinical factors often associated with calciphylaxis include ESRD, female gender, hyper- or hypoparathyroidism, obesity, hyperphosphatemia, hypercalcemia, and the use of vitamin K antagonists (Schlieper et al., 2009).

With the current pathophysiologic concept of heterogenous and ill-defined derangements of mineral metabolism, treatment is aimed at arresting the proposed driving forces of calcification of the medial layer of the small skin arterioles in the hope to stop or reverse disease progression.

1.2 Pathophysiology of calciphylaxis

The development of calciphylaxis can be considered a two-step process: the development of the vascular lesion and the development of tissue ischemia due to the vascular lesion, plus other clinical events (Hanke et al., 2010), as demonstrated in Figure 1.

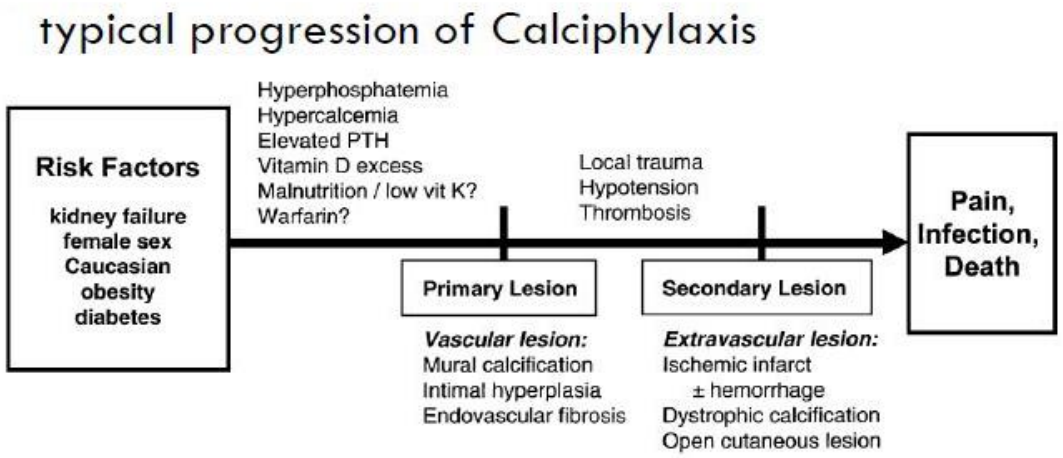

Figure 1: Development of calciphylaxis organ damage

Calciphylaxis affects skin arterioles in the subcutaneous tissue and leads to ischemic skin necroses, often clinically accompanied by opioid-resistant pain and non-healing ulcerations. Histologically, the skin lesions are characterized by medial calcification, endothelial proliferation and luminal thrombosis and are accompanied by a dramatic impairment of skin nutrition and ensuing skin (Brandenburg et al., 2011).

The order of occurrence of the histologic lesions and their potential role in the pathogenesis of calciphylaxis has not been clarified yet. Whereas it seems prudent to assume that the thrombotic occlusion of the vessel lumen is the final step in a cascade of events, it is not clear whether endothelial proliferation and medial calcification do occur concomitantly or sequentially, and if the latter was true – which comes first.

1.3 Conventional treatment options for calciphylaxis patients

Calciphylaxis patients represent by nature a very heterogeneous population with a broad range of calciphylaxis- associated and non-associated medications and diagnoses (as an estimate, the average dialysis patient has 10-15 diagnoses and is on 10-15 different drugs). No standard treatment options for calciphylaxis patients are available.

Treatment modalities, which have been tested so far, are highly variable and all without decisive improvements of the disease course. Amongst others, treatments comprise the cessation of vitamin K antagonists, calcium containing phosphate binders and vitamin D compounds, the lowering of serum phosphate and calcium levels, the use of calcimimetics and of bisphosphonates (Smith et al., 2012), (Veitch et al., 2014). Furthermore, intensified dialysis, meticulous wound care and skin grafting, and even parathyroidectomy have been tried but have not been shown to be convincingly effective (Weenig et al., 2007). The only treatment modality, which was related more constantly with improved pain and wound healing, is the application of hyperbaric oxygen treatment (Benedetto and Emhoff, 2000), (Dean and Werman, 1998) (Benedetto and Emhoff, 2000), which is, however, available in selected centers only.

Apart from these measures, treatment is mainly symptomatic with intensified wound care, and the liberal use of antibiotics and analgesics. Unfortunately, none of these measures alone or in combination has convincingly changed the course and prognosis of calciphylaxis.

1.4 Sodium thiosulfate (STS) for the treatment of calciphylaxis

Sodium Thiosulfate (STS, $Na_2S_2O_3$) is a sulfur salt, which has been used for decades in human medicine and was approved for (i) the treatment of cyanide intoxications (Miller and Toops, 1951) and (ii) as a chemoprotectant against cisplatin-induced oto- and nephrotoxicity (Gandara et al., 1990).

Besides these indications, STS has anecdotally been reported to prevent the progression of nephrocalcinosis (Agroyannis et al., 2001), metastatic calcifications (Papadakis et al., 1996), (Yatzidis, 1985), (Yatzidis and Agroyannis, 1987), kidney stones (Yatzidis, 1985), and coronary artery calcification (Adirekkiat et al., 2010).

In addition, based on theoretical considerations STS has been first used for the treatment of calciphylaxis back in 2004 (Cicone et al., 2004). Case reports in more than 280 patients are available indicating that STS might be beneficial for the treatment of calciphylaxis both in improving the severe pain associated with the condition and in the healing of calciphylaxis lesions (Guerra et al., 2005), (Landau et al., 2007), (Mataic and Bastani, 2006), (Ackermann et al., 2007), (Zitt et al., 2013). Since then, STS has been used off-label for treatment of calciphylaxis but has also been investigated in open label, clinical studies for treatment of other calcifications (e.g. (Adirekkiat et al., 2010).

On 23 February 2011, orphan designation (EU/3/10/848) was granted by the European Medicines Agency (EMA) for sodium thiosulfate for the treatment of calciphylaxis (EMA-COMP, 2011).

The literature documenting the use of STS in the treatment of calciphylaxis is comprehensively reviewed by *Smith et al.*, along with a detailed summary of case reports and case series. Most of these reports documented treatment success, with rapid resolution of pain within days or weeks, often supported by impressive reductions in requirements for analgesia. Cessation of new lesion formation along with complete or partial wound healing or reduction in the size of subcutaneous plaques was also commonly reported. However, most reports described single cases or retrospective analyses of a small number of patients at dialysis centers (Smith et al., 2012), (Zitt et al., 2013), (Salmhofer et al., 2013).

Recently, a retrospective data collection on 172 calciphylaxis patients in centers in the USA over a period of 4 years was reported (Nigwekar et al., 2013). Of these, a complete survey was available for 53 calciphylaxis patients demonstrating substantial improvement in their symptoms. Among surveyed patients, calciphylaxis completely resolved in 26.4%, markedly improved in 18.9%, improved in 28.3%, and did not improve in 5.7% of the patients; in the remaining patients (20.8%), the response was unknown. One-year mortality in patients treated with STS was 35% compared to 60-80% without treatment (Weenig et al., 2007).

1.5 Mode of action of STS

The mode of action of STS is still not completely clarified, however, there are hypothetical models explaining the action of STS in vascular calcification in general, which may be extrapolated to its action in calciphylaxis.

STS appears to have pleiotropic pharmacodynamic properties which might explain its beneficial effects in the diverse spectrum of clinical applications mentioned above. When applied as an antidote in cases of cyanide intoxications, thiosulfate and cyanide are converted to the less toxic thiocyanate by the action of the mitochondrial enzyme thiosulfate sulfurtransferase (TST = rhodanese) (Hildebrandt and Grieshaber, 2008). In contrast, the detoxification of the chemotherapeutic cisplatin is accomplished by the formation of a thiosulfate-cisplatin complex, which prevents the entry of cisplatin into cells and probably facilitates its excretion from the body.

The calcification preventing and anti-ischemic properties of STS, which are probably effective in the treatment of calciphylaxis, may in contrast be due to the following mechanisms of action: (i) chelation/solubilization of calcium (O'Neill, 2008), (ii) induction of an anion gap acidosis (Cicone et al., 2004), (iii) anti-oxidative properties (Hayden and Goldsmith, 2010) (8), (iv) upregulation of calcification preventing proteins (e.g. Matrix GLA Protein [MGP] and fetuin-A) (Pasch et al., 2008), and (v) generation of H_2S, a potent vasodilator (Sen et al., 2008), (Hayden et al., 2008).

Hayden et al. 2005 have formed a hypothesis that the rapid reduction in pain may be due to a restoration of endothelial function associated with this syndrome. The antioxidant effect of STS, given in the i.v. dosing of 12.5–25 grams i.v. at the end of dialysis may help to restore the dysfunctional endothelial cell and begin restoring the endothelium's natural tendency (in health) to produce endothelial nitric oxide (eNO) promoting vasodilation instead of the damaging super oxide and the resultant peroxynitrite (Hayden et al., 2005).

STS may furthermore revert a functional vasoconstriction via the vasodilating molecule H_2S which is likely produced as a consequence of endogenous STS metabolism (Sen et al., 2008). The H_2S-induced dilatation of narrowed skin vessels could also explain the rapid reduction of the (presumably ischemic) pain, which is often seen after the start of STS therapy. The improved oxygen and nutrient supply would then - as in hyperbaric oxygen therapy – support the healing of the ulcerations.

In conclusion, the therapeutic effects of STS are probably mainly due to the neutralization of vasculature-harming reactive oxygen species and the – possibly coupled – generation of a potent vasodilator (H_2S).

The proposed mechanisms of action of STS might thus beneficially affect both, the medial calcifications and the vascular luminal narrowing. The potential of inhibition of calcium precipitation and calcium chelation is probably rather a contributing therapeutic effect of STS.

1.6 Pharmacokinetics

Thiosulfate (TS, $S_2O_3^{2-}$), the anion of STS, is an endogenous intermediate of mammalian sulfur metabolism. The endogenous synthesis of TS is accomplished by three mitochondrial enzymes, sulfur-quinone oxidoreductase (SQR), ethylmalonic encephalopathy 1 (ETHE1) and the TST enzyme (Hildebrandt and Grieshaber, 2008). The physiological excretion of TS is in the range of 10-20 µmol/day in the urine of healthy persons and depends on protein intake and likely on genetic factors (Farese et al., 2011).

Because of the free filtration of STS in the renal glomerulum, the negligible tubular handling, its low protein binding and the distribution in the extracellular space, STS was widely used as an alternative to inulin clearance measurement for the routine determination of kidney function in the 1940s to 1970s (Vorburger et al., 1969).

There are only few data on the pharmacokinetics in humans available in the literature.

In healthy volunteers, STS is poorly absorbed orally, but is rapidly distributed throughout extracellular fluid after i.v. administration. STS taken orally is not systemically absorbed. Most of the thiosulfate is oxidized to sulfate or is incorporated into endogenous sulphur compounds; a small proportion is excreted through the kidneys. Approximately 20-50% of exogenously administered STS is eliminated unchanged via the kidneys. The volume of distribution of STS is 150 mL/kg. STS is excreted in the urine, with a clearance half-life of 0.25 to 3 hours being reported when a single bolus dose of 1 g of STS is given. However, after an i.v. injection of a substantially higher dose of STS (150 mg/kg, that is, 9 g for 60 kg bw) in normal healthy men, the reported elimination half-life was 182 minutes (for details, see Investigator's Brochure).

In the absence of an intact kidney function (i.e. in dialysis patients) STS is completely metabolized endogenously and the resulting sulfate is largely removed during the next dialysis session (Farese et al., 2011). Therefore and because of a better tolerability, start of infusion of STS is recommended 30 min before the end of hemodialysis (HD) with an overall infusion duration of 60 min.

1.7 Safety profile

STS has been used in human medicine for decades. In the 1950s and 1960s it was used for the determination of renal function. An assessment of the periodic safety update reports (PSUR) since the international birthdate of STS in 1978 in Germany did not reveal critical side effects such as acute poisoning, death or any deterioration of the patient that required admission to a hospital. This assessment includes data from 24 human studies comprising more than 1,200 patients who have been treated with STS as a cancer chemoprotectant primarily for the prevention of cisplatin-induced ototoxicity.

STS seems to have an acceptable safety profile and is usually well tolerated. The most prominent side effects reported with STS are nausea and vomiting, often in patients treated with a dose of 25 g 3x per week, and are usually described as mild, temporally related to the infusion, and responsive to antiemetics and/or prokinetics. Reducing the dose or rate of infusion can be helpful. A raised anion gap metabolic acidosis is also well recognized, and can be severe (Selk and Rodby, 2011; Mao et al., 2013). This is again less of a problem with a reduced dose, but is also relatively easily managed with bicarbonate supplementation or increasing the dialysate bicarbonate.

Headache, hypotension, thrombophlebitis (when STS is given through a peripheral i.v. cannula), and hypersensitivity to smells with anorexia have been reported (Baker et al., 2007), (Musso et al., 2009), (Ong and Coulson, 2011), (Tokashiki et al., 2006).

With regard to longer-term adverse effects, there is some concern regarding the possibility of bone demineralization, with a reduction in bone strength/bone mineral density (BMD) compared with controls reported in both animal and human studies of STS. *Adirekkiat et al.* demonstrated a significant reduction in total hip BMD and a trend towards a reduction in lumbar spine BMD in 15 patients treated with 12.5 g i.v. STS twice weekly for 4-months

(Adirekkiat et al., 2010). This dose is within the dose range usually given for the treatment of calciphylaxis (6-25 g for 3x per week). The reason for the reduction in BMD is unclear, but the metabolic acidosis induced by STS treatment was proposed as a contributing factor. Another study in 22 haemodialysis patients could not detect any reduction in lumbar BMD after STS treatment for 5 months (Mathews et al., 2011). Although reports from the literature regarding bone-demineralisation effects of STS are contradictory, any bone fractures in longer-term survivors of calciphylaxis patients treated with STS should be observed and thoroughly monitored.

No other serious side effects have been reported despite the long clinical use of STS.

1.8 Animal proof-of-concept studies with sodium thiosulfate in calciphylaxis

No animal model of calciphylaxis is available. However, *Pasch et al.* used a rat model of renal failure based on addition of adenine to the diet, which produces severe interstitial nephritis and uremia, with medial vascular calcification developing within 4 weeks (Pasch et al., 2008). STS prevents calcification in this model at a dose and interval comparable to those used in humans with calciphylaxis/CUA, thus providing a scientific basis for its clinical use. This model of renal failure is associated with marked polyuria and salt wasting rather than oliguria and sodium retention in dialysis patients, which could differentially affect STS levels and calcium balance.

The authors determined whether it also prevents development of vascular calcifications in chronic kidney disease (CKD). They found inter alia that uremic rats treated by STS had no histological evidence of calcification in the aortic wall whereas almost three-fourths of untreated uremic rats showed aortic calcification. Urinary calcium excretion was elevated and the calcium content of aortic, heart and renal tissue was significantly reduced in the STS-treated compared to non-treated animals. STS treatment transiently lowered plasma ionized calcium and induced metabolic acidosis. It also lowered bone strength in the treated animals compared to their normal controls. Hence, STS prevented vascular calcifications in uremic rats, likely by enhancing acid- and/or chelation-induced urinary calcium loss (see also Investigator's Brochure).

As mentioned above, no animal model for calciphylaxis is available and therefore, the pathophysiology and histology of calciphylaxis need to be studied in human biopsies, in which calcifications can be detected. As no biopsy study has been conducted longitudinally in calciphylaxis so far, neither the putative role of media calcification nor the sequence of the occurence of the typical histologic lesions intimal proliferation, medial calcification and luminal thrombosis of the small skin vessels have been elucidated yet. Consequently, the questions whether calcification is the *primum movens* or a consequence of ischemic changes induced by intimal proliferation and luminal thrombosis awaits clarification.

2 RATIONALE

2.1 STS for the treatment of calciphylaxis

Up to now, no prospective clinical trial with STS has been performed. Reasons are that calciphylaxis is a rare condition and treatment is not focused on certain centres making feasibility studies nearly impossible. Due to the limited number of patients and the spontaneous occurrence of the disease, the recruitment of calciphylaxis patients is challenging.

The previous case reports on successful treatments of calciphylaxis patients with STS support the intention to demonstrate the efficacy and safety of STS in this patient population under the conditions of a prospectively planned clinical trial.

2.2 Rationale for the dose of STS

Studies on safety and efficacy of various STS doses and on the treatment duration of STS are not feasible in calciphylaxis due to the heterogeneity and paucity of patients.

The application of doses in the range of 12.5 to 25 g has been reported in most publications on calciphylaxis patients. This dose range is based on the experience with STS as antidote for cyanide poisoning and extravasation of chemotherapeutic agents.

Only few case reports are available on the treatment of cyanide poisoning. The dose range reported for these cases was 8-12.5 g or 0.2 g/kg bodyweight, administered as bolus injection or infusion. The treatment duration was up to 12 h.

For extravasation of chemotherapeutic agents (cisplatin), publications on more than 1200 patients are available with a dose range of 3-20 g/m^2 body surface area. Lower doses were infused over 3 to 15 min, higher doses were infused over several hours. The treatment duration was up to 12 h.

Case reports and cohort studies with more than 300 calciphylaxis patients have been published up to now (see also Investigator's Brochure). In the majority of reports, a dose of 25 g per day was used (see Investigator's Brochure, Table 14). Infusion occurred during 30-

60 min at the end or after HD. Treatment duration was up to 62 weeks. On this basis, 25 g per day 3x per week was selected as an effective starting dose. To start with lower and potentially ineffective doses is ethically not acceptable for these patients. It was observed that flares may occur after reduction to 12.5 g or less, requiring subsequent increase of the STS dose to induce improvement (Pasch, personal communication). Reduction of pain is considered a very good indicator of efficacy in calciphylaxis. Therefore, the individual dosing scheme was reported to often be adjusted based on pain response, which is usually achieved within two to three weeks after the first administration.

In the present clinical trial, the dose of 25 g will be administered i.v. as an infusion starting 30 min before end of HD over 60 min 3x per week. In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms.

In case of complete remission of the wound lesion after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4) the dose may only be reduced for safety reasons.

Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed.The change in dose is at the discretion of the investigator.

3 OBJECTIVE, STUDY DESIGN AND STUDY DURATION

The objective of this project is to study the potentially beneficial effects of STS on the course and outcome of calciphylaxis. The study population will consist of 40 patients ≥ 18 years of age with calciphylaxis. Patients will be treated with STS for at least 24 weeks. It is up to the discretion of the investigator to continue STS treatment.

The study design is a prospective, uncontrolled, multicenter, Phase 2/3 study including dialysis centers in -Europea(~~Switzerland, Germany, Austria, France~~).

The duration of the trial for each patient is expected to be up to 48 weeks plus the preceding 2 to 4 weeks run-in period.

The overall duration of the trial is expected to be approximately 4 years. The actual overall duration or recruitment may vary.

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint:

- Percent reduction of the total wound area after 24 weeks (V4) compared to baseline (V0) as assessed by 2 independent, blinded dermatologists using a serial photo documentation. The mean value of both assessments will be taken.

3.1.2 Secondary Endpoints:

- <u>Status of skin lesions:</u>
  - Total wound area at 8, 16, 36, 48 weeks compared to baseline (V0).
  - Complete remission of wound area.
  - Occurrence of new lesions: Time point of occurrence and – if applicable – healing as well as location of each lesion to be documented at each visit (V0 to V6).
  - Qualitative improvement of skin lesions at 8, 16, 24, 36, 48 weeks as assessed by the revised Photographic Wound Assessment Tool (revPWAT) score and evaluation of a serial photo documentation through 2 independent, blinded dermatologists.
  - Use of wound debridement

- Pain:
  - Reduction of pain in the areas of calciphylaxis after 4, 8, 16, 24, 36 and 48 weeks after start of STS treatment will be compared to baseline (V0) and assessed by a visual analogue scale (VAS) for pain (0-10). This will be done directly before changing the wound dressing.
  - Consumption of pain medication (normalized to morphine equivalent with an appropriate conversion table) will be assessed at VR, V0 and 4, 8, 16, 24, 36 and 48 weeks after start of STS treatment and compared to baseline (V0).
- Clinical global impression:
  - Change in clinical global impression as assessed by the Clinical Global Impressions-Improvement (CGI-I) score at each follow-up visit (after 4, 8, 16, 24, 36 and 48 weeks) compared to baseline (V0) and the Clinical Global Impression-Severity scale (CGI-S) through the investigators. The Clinical Global Impression-Severity scale (CGI-S) will be assessed at each visit from visit V0 to V6 (i.e. after 4, 8, 16, 24, 36 and 48 weeks).
- Improvement leading to eligibility of the patient for kidney transplantation:
  - Eligibility for kidney transplantation is given when the patient is being actively listed on a transplant waiting list.
- Bone mineral density (BMD):
  - For measurement of BMD, study sites will be evaluated for the availability of Dual Energy X-ray absorptiometry (DEXA) technique.
  - BMD will be measured at V0 and after 48 weeks (V6)
- Survival:
  - Median overall survival after start of STS treatment
  - One-year survival rate

3.1.3 Safety parameters:

- Adverse events
- AESI (incidence of infections and sepsis, metabolic acidosis, ventricular tachycardia, hypotension, bone fractures)
- Use of other concomitant medications
- Laboratory parameters (parathyroid hormone [PTH], total calcium, phosphorus, alkaline phosphatase, pH, CRP, leucocytes, hemoglobin, creatinine, albumin, Na, K, Cl, Mg, ASAT, ALAT, GGT, Amylase, Lipase, urea, uric acid, venous blood gas analysis, 1.25 vitamin D, 25 vitamin D,
- Physical examinations, ECG, vital signs (heart rate, blood pressure)

Tolerability of STS treatment

3.1.4 Biobanking

- Serum will be collected for assessing further relevant parameters, e.g. inflammatory and calcification parameters and bone turn-over markers. The evaluation of these parameters is planned to be performed within 5 years after the end of the trial.
- T50 test (in vitro blood test for calcification propensity by monitoring the maturation time (T50) of calciprotein particles in serum according to Pasch et al. (Pasch et al., 2012).

3.2 Number of patients

We aim to include a total of 40 patients in this study. Recruitment and treatment of patients is planned to be performed in dialysis centers. Further sites might be selected during the active period of the trial.

3.3 Diagnosis

At start of the run-in phase (VR) and during the run-in phase, patients will be examined by serological and histological parameters as indicated to confirm the diagnosis of calciphylaxis and to exclude other causes for necrotizing skin lesions and ulcerations.

The following differential diagnoses should be considered depending on clinical circumstances:

- peripheral arterial occlusive disease
- vasculitis
- arterial embolism
- anti-phospholipid antibody syndrome
- coumarin necrosis
- cryoglobin-related skin disorder
- heparin necrosis
- nephrogenic systemic fibrosis

The following diseases and conditions have to be excluded histologically:

- Pyoderma gangraenosum
- coumarin necrosis
- nephrogenic systemic fibrosis

If the typical clinical signs for calciphylaxis are detected, in particular more than one lesion appears, and other diagnoses can be excluded based on the results of serological and histological analyses, the diagnosis of calciphylaxis can be confirmed.

3.4 Medications and measures for best supportive care

The following measures for best supportive care (BSC) are considered obligatory:

- Cautious necrosectomy only, no debridement of wound margins!
- Keep patients dry and treat peripheral edema to support wound healing

The following measures are considered as optional and are proposed in the literature as potential treatments for calciphylaxis patients. It is at the discretion of the trial centers respectively the investigators, which measures are appropriate for treatment during the run-in phase. However, all participating centers are free in their decision how to treat their calciphylaxis patients during the run-in phase:

- Reducing ionised Ca^{2+} and PO_4^- to the lower normal range
- Stopping vitamin D compounds (25-OH, 1,25-OH, paricalcitol)
- Replacement of calcium-containing phosphate binders
- Treatment of patients having hyperparathyreoidism with high bone turnover (high alkaline phosphatase) with parathyreoidectomy or Cinacalcet
- Stopping coumarine
- Replacing coumarine with low molecular weight heparins
- Administration of vitamin K
- Avoidance of iron therapy i.v./p.o.
- Reducing skin punctures and other tissue traumata to a minimum
- If applicable, surgical therapy /plastische cover of the lesion
- Permanent administration of antibiotics
- Avoidance of phosphate-containing enemas (contraindicated in patients with renal insufficiency)
- In case of peritoneal dialysis, switch to HD
- HD eKt/V at least 1.2
- Switch to HD during daytime or long nocturnal HD
- Switch to HDF
- Dialysis against low calcium dialysate (1.25 mmol/L or lower)
- Plasmapheresis against fresh frozen plasma (FFP)
- Hyperbaric oxygen

3.5 Study treatment

At start of the run-in phase (VR) of 2 to 4 weeks, patients will be treated with conventional medications and measures as described in section 3.4. Considering the severity of the disease, the run-in period has to be limited to 2 weeks for those patients rapidly progressing under BSC while for the other patients a 4-week run-in phase is justifiable.

If the investigator observes typical symptoms of calciphylaxis (e.g. pain, appearance of more than one wound lesion) and decides that the patient is eligible for the treatment with STS and participation in the clinical trial, a biopsy will be taken to confirm the diagnosis of calciphylaxis by excluding other causes of necroses and ulcerations. If a biopsy report of a consisting wound is available at Screening (VR) and the diagnosis of calciphylaxis is confirmed or other causes for necroses and ulcerations were excluded, an additional biopsy is not required. Patients with rapidly progressive disease under BSC will be allocated to Group A while patients with less progressive or initially stable disease will be allocated to Group B. Patients in both groups will be treated with STS. Both patient groups will be analysed separately, with Group A to establish efficacy and Group B to be assessed descriptively (see section 11.2.1). Patients with severe disease status may be switched to STS treatment earlier than 2 weeks. These patients will be excluded from the Per-Protocol (PP) analysis.

Then, at V0, treatment with STS starts and will be continued for at least 24 weeks. From the long-standing experience published in the literature, a clinically meaningful reduction (>20%) in the total wound area is expected by the clinical experts after 24 weeks of STS treatment.

The dose of 25 g will be administered i.v. as an infusion starting 30 min before end of HD over 60 min 3x per week. In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms.

In case of complete remission of the wound area after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4) the dose may only be reduced for safety reasons.

Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed. The total amount of STS administered over all treatments will be calculated and recorded for each visit.

It is at the discretion of the investigator to reduce the dose to a lower dose in case of adverse effects. Treatment will continue up to 48 weeks until either complete remission, reduction in pain, reduction in wound surface, healing of ulcera, or discontinuation due to side effects occurs.

3.6 Definition of treatment response

For patients treated with BSC, wound size is typically increasing as shown in the literature and medical expert knowledge. A median reduction of the total wound area of 20% or more is clearly a clinically relevant improvement as, again based on empirical medical knowledge, wound size is correlated with the detrimental symptoms of calciphylaxis. For the current study, a median wound size reduction of 50% or more is expected.

3.7 Safety Monitoring

Safety assessments start at the time point, when the patient enters the run-in phase (VR).

If the patient is excluded from the trial at baseline (V0) because the diagnosis of calciphylaxis cannot be confirmed or because the patient withdraws the consent for STS treatment, the patient will not be followed up in the trial beyond that time point for further assessments of safety parameters.

Safety parameters will include adverse events, concomitant pain and other medications, physical examinations, ECG, vital signs, standard clinical laboratory evaluations (as described in section 3.1.2), and tolerability of STS treatment.

4 PATIENT SELECTION

4.1 Inclusion Criteria

(1) All patients ≥ 18 years

(2) Male or female HD patients with a diagnosis of calciphylaxis. (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching).

(3) Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study

4.2 Exclusion Criteria

(1) Females who are pregnant (positive pregnancy test at screening or during study phase), lactating, or, if having reproductive potential (being not post-menopausal* or surgically sterilized) are considered potentially ineligible with respect to use highly effective** methods of birth control throughout the study, which are also described in detail in the Patient Inform Consent Form. (Of note, STS has been demonstrated not to cross the blood-placenta barrier in gravid eves (Graeme et al., 1999); therefore we regard fetal damage also as unlikely in humans).

(2) Patients who have participated in any other investigational studies within 30 days previous to enrollment

(3) History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment.

(4) Good response to conventional treatment.

(5) Life expectancy less than 4 months in the judgement of the investigator

*: Post-menopausal: no menses for 12 months without an alternative medical cause

**: Highly effective methods of birth control: methods that alone or in combination result in a failure rate less than 1% per year when used consistently and correctly. A combination of two of the following methods is considered highly effective:
a) use of oral, injected or implanted hormonal methods of contraception (in the case of oral contraception, the same pill at the same dosage for at least 3 months before taking the study medication)
b) placement of an intrauterine device (IUD) or intrauterine system (IUS)
c) use of barrier methods (diaphragm or cervical cap, which are not made of latex) in women, or the use of a condom by male partner in combination with a spermicidal foam/gel/coating/cream/vaginal suppository

4.3 Concomitant medications

All medications taken by the patients for treatment of the symptoms of calciphylaxis during the run-in phase and the subsequent STS treatment phase will be recorded in the eCRF with actual dose, duration of treatment and indication up to 48 weeks.

4.4 Patient Withdrawal

Patients are free to withdraw from the study at any time for any reason. In addition, patients may be withdrawn from the study by the Principal Investigator or Sub Investigator for the following reasons:

- Adverse events (e.g. uncontrollable infections, pain, nausea),
- progression despite treatment,
- severity of the disease

The clinical report will include reasons for patient withdrawals as well as details relevant to the patient withdrawal. If a patient is withdrawn from the trial prior to study completion, he/she will undergo all procedures scheduled for study completion

4.5 Premature Closure of the Clinical Trial

The trial can be prematurely closed or suspended by the Coordinating Investigator or the sponsor in case that new risks for patients become known. The Ethics Committee (EC) and the competent regulatory authorities must then be informed. Furthermore, the EC and competent regulatory authorities themselves may decide to stop or suspend the trial.

Should the trial be closed prematurely, all trial material (investigational medicinal products, etc.) must be returned to the Sponsor.

All involved investigators have to be informed immediately about a cessation/ suspension of the trial. The decision is binding to all trial center's and investigators.

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4.6 Treatment Assignment

The trial medication will be administered only to patients included in this trial.

Patients withdrawn from the trial retain their identification codes. New patients must always be allocated a new identification code.

4.7 Dosing of the study medication

At start of the run-in phase (VR) of 2 to 4 weeks, patients will be treated with conventional medications and measures as BSC (see section 3.4). If the investigator observes typical symptoms of calciphylaxis (e.g. pain, appearance of more than one wound lesion) and decides that the patients is eligible for the treatment with STS and participation in the clinical trial, a biopsy will be taken to confirm the diagnosis of calciphylaxis by excluding other causes of necroses and ulcerations. If a biopsy report of a consisting wound is available at Screening (VR) and the diagnosis of calciphylaxis is confirmed or other causes for necroses and ulcerations were excluded, an additional biopsy is not required. Then, patients will be treated with STS (V0).

The dose of 25 g will be administered i.v. as an infusion starting 30 min before end of HD over 60 min 3x per week. In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms.

In case of complete remission of the wound lesion after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4) the dose may only be reduced for safety reasons.

Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed in the eCRF.

It is at the discretion of the physician to reduce the dose to the next-lower dose in case of adverse effects.

Treatment will continue up to 48 weeks (V6) until either complete remission, reduction in pain, reduction in wound surface, healing of ulcera, or discontinuation due to side effects occurs.

4.8 Packaging and Labelling

The trial medication will be labelled according to GCP requirements.

4.9 Supplies and Accountability

The investigator will keep an account of the trial medication and acknowledge the receipt of all shipments of the trial medication.

The investigator will also keep accurate records of the quantities of trial medication used for each patient. The documentation has to include date of application, patient identification, batch/ serial numbers or other identification of trial medication. The site monitor will periodically check the supplies of trial medication held by the investigator to ensure the correct accountability of all trial medication used. At the end of the trial, all unused trial medication and all medication containers will be completely returned to the sponsor. It will be assured that a final report of the drug accountability is prepared and maintained by the investigator.

5 CONDUCT OF THE TRIAL AND STUDY ASSESSMENT SCHEDULE

The study shall be performed according to the following chronological steps, which are depicted hereafter and in Figure 1 and Flow Chart (Table 1).

5.1 Identification and inclusion of a calciphylaxis patient in the trial center

Patients with calciphylaxis are typically identified in dialysis centers.

A first diagnosis of suspected calciphylaxis will be performed according to the typical signs and symptoms (severe pain, livedo, violaceous plaques, ulcerations, necroses) and by excluding other causes of necroses and ulcerations as described in section 3.3.

Each patient will be identified by a 7-digit patient number, which is a combination of the 2-digit county number, the 2-digit site number and a unique 3-digit number. The country number (eg 01, 02 etc.) and site number (eg 01, 02 etc.) will be assigned by the CRO, the unique 3-digit number will be assigned to the patient by the investigator, starting with 001. For example, the patient number for the first patient in country 01 at site 01 will be 01-01-001.

At start of the 2 to 4-week run-in phase (VR), the patient will be informed about the character and individual consequences of the clinical trial and has to provide written informed consent to participate in the study.

Upon decision of eligibility of the patient to participate in this clinical trial by fulfilling all inclusion and no exclusion criteria, the diagnosis, medical history and demographic data, including sex, age, race, body weight (kg), height (cm), BMI and tobacco use will be recorded in the eCRF. Each patient will have a physical examination, vital sign measurements (heart rate, blood pressure, ECG), and the laboratory tests. Then, the patient will be treated with conventional medications and measures (see section 3.4).

If the investigator assesses the patients as eligible for the treatment with STS, a biopsy will be taken and analyzed during the run-in phase to confirm the diagnosis of calciphylaxis by excluding other causes of necroses and ulcerations. Additionally at the end of the study all biopsy samples will be analyzed centrally.

When the diagnosis of calciphylaxis has been confirmed, the patient will be asked again if he/she agrees to participate in the clinical trial and to undergo STS treatment.

The run-in phase will end on the same day, when patients will start treatment with STS (baseline, V0).

5.2 Photo documentation and assessment of the wound area

Photo documentation of all skin lesions (total wound area) will be performed at VR, V0 (baseline), V2 (8 weeks), V3 (16 weeks), V4 (24 weeks), V5 (36 weeks) and V6 (48 weeks, end of study) to follow progression as well as remission. A graded straight edge including a colored scale will be added at the edge of the wound. The photographs will be taken under common circumstances in the in-and outpatient departments without any additional light sources; flash light should be avoided if possible. On the photographs, the necrosis/ulcers and the surrounding skin will be included.

To avoid possible bias in the assessment of the wound area, it is important to choose a camera position perpendicular to the approximate center of the wound. The distance between camera and wound should be about 50 centimeters. This distance should not even be decreased for small wounds as smaller distances lead to image distortions especially if the wounds are located on curved surfaces. Instead, the zoom of the camera should be used as it does not create this type of distortions.

Nevertheless, wounds on strongly curved surfaces (arms, etc.) may not fit one photograph. In this case, several images of the same wound should be taken. To allow the later area assessment, pencil marks (for example small arrows) should be placed on the healthy skin at the border on the wound before the photographs are taken to denote, which part of the wound gets measured on image 1 and which on image 2.

For the measurement of the skin lesion, the inner edge of the wound will be taken. The area of each lesion will then be analyzed using the software package ImageJ.

An example is provided in Figure 2 demonstrating the assessment of the wound area in a calciphylaxis patient at start of STS treatment (calculated area is 68.6 cm^2).

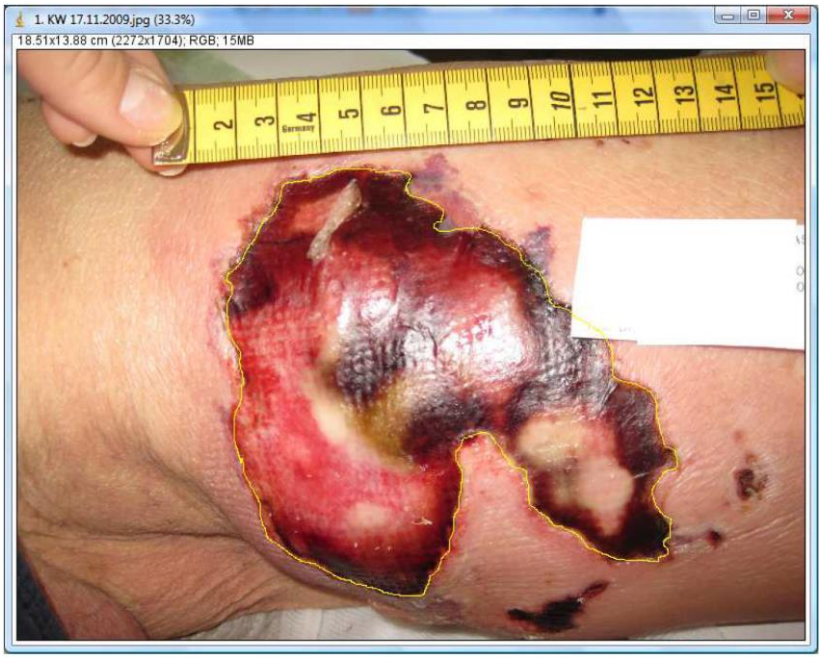

Figure 2: Photograpic documentation and assessment of wound area with the ImageJ software at start of STS administration in calciphylaxis patients

Changes in the appearance of the wounds will be assessed on the photographs by the blinded dermatologists using the revPWAT score (Thompson et al., 2013). This validated score consists of 8 domains with possible scores ranging between 0 and 32, with zero representing a completely healed wound (Figure 3). In case of missing efficacy scores (e.g. patient passes away or withdraws from the trial at later time points), the missing values will be imputed as described in 11.2.4 and the patient will be included in the efficacy analysis.

Figure 3: Photographic Wound Assessment Tool – revised (revPWAT)

Item	Assessment	Score
1. Size	0 = wound is closed (skin intact) or nearly closed (<0.3 cm^2) 1 = 0.5 – 2.0 cm^2 2 = 2.0 – 10.0 cm^2 3 = 10.0 – 20.0 cm^2 4 = > 20.0 cm^2	
2. Depth	0 = wound is healed (skin intact) or nearly closed (<0.3 cm^2) 1 = full thickness 2 = unable to judge because majority of wound base is covered by yellow/black eschar 3 = full thickness involving underlying tissue layers 4 = tendon joint capsule visible/bone present in wound base	
3. Necrotic tissue type	0 = none visible or wound is closed (skin intact) or nearly closed (<0.3 cm^2) 1 = majority of necrotic tissue is thin white/gray or yellow slough 2 = majority of necrotic tissue is thick, adherent white yellow slough or fibrin 3 = majority of necrotic tissue is white/grey devitalized tissue or eschar 4 = majority of necrotic tissue is hard grey to black eschar	
4. Total amount of necrotic tissue	0 = none visible in open wound or wound is closed (skin intact) or nearly closed (0.3 cm^2) 1 = < 25% of wound bed covered 2 = 25% to 50% of wound covered 3 = > 50% and < 75% of wound covered 4 = 75% to 100% of wound covered	
5. Granulation tissue type	0 = wound is closed (skin intact) or very close to closed (<0.3 cm^2) 1 = majority (>50%) of granulation tissue is healthy looking (even, bright red appearance) 2 = majority of granulation tissue is unhealthy (eg, pale, dull, dusky, hypergranulation) 3 = majority of granulation tissue is damaged, friable, degrading 4 = there is no granulation tissue present in the base of the open wound (all necrotic)	

Figure 3: continued

6. Total amount of granulation tissue	0 = Wound is closed (skin intact) or very close to closed (<0.3 cm^2) 1 = 75% to 100% of open wound is covered with granulation tissue 2 = >50% and <75% of open wound is covered with granulation tissue 3 = 25% to 50% of wound bed is covered with granulation tissue 4 = <25% of wound bed is covered with granulation tissue			
7. Edges (directly touching and within 0.5 cm of wound edge)	0 = Wound is closed (skin intact) or very close to closed (<0.3 cm^2) or edges are indistinct, diffuse, not clearly visible because of re-epithelialization 1 = majority of edges (>50%) are attached with an advancing border of epithelium 2 = majority of edges (>50%) are attached even with wound base (not advancing) 3 = majority of edges(>50%) are unattached and/or undermined 4 = majority of edges are rolled, thickened or fibrotic (do not include callus formation)			
8. Periulcer skin viability (consider skin visible in photo or within 10 cm of wound edge)	Number of factors affected 0 = None 1 = One only 2 = 2 or 3 3 = 4 or 5 4 = 6 or more	• callus • dermatitis • maceration • desiccation or cracking • bright red erythemic	• edema • excoriation • skin tearing/irritation related to wound dressing or tape • hypo-/hyperpigmentation • other: _____	
Total score				

5.3 Biopsy taking and histological assessment

A biopsy will be taken a few days before the end of the run-in phase to confirm the diagnosis of calciphylaxis by excluding other causes for necroses and ulcerations. If a biopsy report of a consisting wound is available at Screening (VR) and the diagnosis of calciphylaxis is confirmed or other causes for necroses and ulcerations were excluded, an additional biopsy is not required.

Spindle shapes skin biopsies will be taken in the participating centers by excision of an approximately 2 x 0.6 cm spindle-shaped piece of skin, radially involving healthy and calcified plaque-like skin, or healthy skin and the border of an ulcerative lesion.

Alternatively, a deep 5 mm punch biopsy will be taken from the border of the affected skin area. The biopsy wound can thereafter stay open or should be closed by a surgical suture, depending on heaviness of bleeding.

The biopsy will be analyzed by Alzain and Kossa stainings to detect calcification and thus, to confirm the condition of calciphylaxis or for exclusion of other causes of necrosis and/or ulceration of the skin.

5.4 Assessment of Bone Mineral Density (BMD)

The contract research organisation (CRO) performing the initiation of the study sites and monitoring for the clinical trial will evaluate the availability of DEXA scanners and the possibility to use this technique for determining the BMD in calciphylaxis patients at baseline (V0) and after 48 weeks (V6).

Dual **E**nergy **X**-ray **A**bsortiometry, or DEXA scanning, is currently the most widely used method and the most reliable technique for measurement of bone mineral density (BMD) for several reasons. DEXA is the clinical standard for measurement of BMD. DEXA scanners use an X-ray rather than gamma ray source to emit dual energy photons. The advantages of this technique are shorter scan time, lower radiation exposure (less than 3 mRem), higher precision and less expensive. DEXA scanning is more sensitive and accurate at measuring subtle changes in bone density over time or in response to drug therapy than is Qualitative computed tomography (QCT).

For the test, a patient lies down on an examining table, and the scanner rapidly directs x-ray energy from two different sources towards the bone being examined in an alternating fashion at a set frequency. BMD will be measured in the hip and spine. In certain situations – e.g. if the hip or spine cannot be measured - BMD will be measured in the forearm. The mineral density of the patient's bone weakens, or prolongs the transmission of these two sources of x-ray energy through a filter onto a counter in a degree related to the amount of bone mass present. The greater the bone mineral density, the greater the signal picked up by the photon

counter. The use of the two different x-ray energy sources rather than more traditional radioisotope studies (such that would be used for a bone scan) greatly improves the precision and accuracy of the measurements.

5.5 Administration of STS

Upon confirmation of the condition of calciphylaxis by analysis of the biopsy, STS will be administered i.v. as an infusion over 60 min 3x per week by starting 30 min before end of HD at V0 (baseline).

In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms.

In case of complete remission of the wound lesion after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4), the dose may only be reduced for safety reasons.

Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed in the eCRF.

The association of the total amount of administered study drug and the treatment effect will be plotted and analyzed using a linear regression model.

5.6 Documentation of pain on a visual analogue-pain scale

Degree of pain will be assessed at start of the run-in phase (VR), at baseline (V0), and directly before changing wound dressings at 4 (V1), 8 (V2), 16 (V3), 24 (V4), 36 (V5) and 48 weeks (V6). The patient has to indicate his/her experience of present pain in the area of the wound lesions on a visual analogue scale (VAS) (0-10, i.e. no pain (=0) to worst pain imaginable (=10)).

A 10-20% decrease in pain intensity is considered minimally important, at least 30% decrease is moderately important, and more than 50% decrease is a substantial improvement (Breivik et al., 2008).

5.7 Documentation of pain medication and other concomitant medications

All participating centers are – apart from the study medication – free in their decision how to treat their calciphylaxis patients. This means that all therapeutic measures can be applied according to BSC at the participating center. These measures including concomitant medications have to be documented in the eCRF at each dialysis visit before start of dialysis.

Consumption of pain medication will be normalized to morphine equivalent with an appropriate conversion table and will be assessed at each visit, at which the VAS will be assessed (VR, V0 and after 4, 8, 16, 24, 36 and 48 weeks).

5.8 Treatment success/change in clinical global impression

After 24 weeks (V4), appraisal of therapy success will be assessed by photo documentation of the wound status, measurement of total wound area, and assessment of pain, as indicated in Section 3.1.1 primary endpoints.

- The changes in the clinical global impression will be assessed by the Clinical Global Impression-Severity scale (CGI-S) and the Clinical Global Impressions-Improvement (CGI-I) score according to Busner and Targum (Busner and Targum, 2007). The CGI-S rates the severity of the patient's illness at the time of assessment, the CGI-I allows to quantify and track patient progress and treatment response over time. The CGI-Sscale will be assessed for the first time at baseline (V0). TheCGI-I will then be assessed at each follow-up visit (V1-V6) and will be compared to baseline CGI-S. The Clinical Global Impression-Severity scale (CGI-S) will be assessed at each visit from visit V0 to V6. The following query is rated on a seven-point scale:

"Considering your total clinical experience with this particular population, how ill is the patient at this time:

1= normal, not at all ill;

2=borderline mentally ill

3=mildly ill;

4=moderately ill;

5= markedly ill;

6=severely ill;

7=extremely ill."

"Compared to the patient's condition at the baseline visit (V0), this patient's condition is:

1=very much improved since the initiation of treatment;

2=much improved;

3=minimally improved;

4=no change from baseline (the initiation of treatment);

5=minimally worse;

6= much worse;

7=very much worse since the initiation of treatment."

5.9 Eligibility of the patients for kidney transplantation

Eligibility for kidney transplantation is given when the patient is being actively listed on a transplant waiting list.

5.10Occurrence of new lesions

The time point of occurrence and – if applicable – healing as well as the location of eachlesion will be documented in the eCRF. In order to ensure traceability of the lesions each

lesion will receive at time of occurrence a consecutive number (L1 to LX) which will be maintained throughout the study.

5.11Follow-up period up to 48 weeks

If tolerated by the patient, the dose of 25 g 3 x per week should be applied up to 24 weeks (V4) to assess the efficacy of this dose for the primary endpoint. During the continuing period up to 48 weeks, either continuation or slow reduction of STS dosing may occur as needed by the patient or in case of complete wound healing after at least 24 weeks of treatment. If cessation of STS is decided by the investigator for safety reasons (allowed at any time) or because of complete wound healing (only allowed after 24 weeks of treatment), a restart of STS treatment is possible in case of flares and recurrence of symptoms. Each change in dosing, stop of administration of STS and restart of STS treatment has to be recorded in the eCRF.

5.12Laboratory parameters

At start of the run-in phase (VR), at baseline (V0), and after 8, 16, 24 and 48 weeks, blood sampling and freezing of a 10 ml serum vial directly before dialysis has to be performed for analysis of laboratory parameters (PTH, total calcium, phosphorus, alkaline phosphatase, pH, CRP, leucocytes, hemoglobin, creatinine, albumin, Na, K, Cl, Mg, ASAT, ALAT, GGT, Amylase, Lipase, urea, uric acid, venous blood gas analysis (pH, pO_2, SB), 1.25 vitamin D, 25 vitamin D). Analysis of these blood parameters will be performed locally at the respective study site.

The T50 test will be conducted to obtain information on the calcification propensity by monitoring the maturation time (T50) of calciprotein particles in serum (Pasch et al., 2012). For this test, about 2 ml blood samples (serum) will be taken at the respective time points (VR, at baseline (V0), and after 8, 16, 24 and 48 weeks). Labelled tubes will be provided to the study site by the central laboratory. The analysis of the samples will be done within 5 years after end of study by the company Calcisco AG, Switzerland. Remaining samples will be destroyed at the Calcisco AG.

For establishing a biobank for calciphylaxis, blood samples (serum) will be analyzed for relevant parameters, e.g. inflammatory and calcification parameters and bone turn-over markers At each time point of blood sampling (see above), additionally 10 ml serum will be taken. Labelled tubes will be provided to the study site by the central laboratory..

All samples will be shipped on dry ice to the central laboratory on the day of collection and are stored centrally at -80°C until analysis will be performed.

5.13Soft tissue radiographs - optional

It is optional, i.e. at the discretion of the investigator to take soft tissue radiographs using mammography x-ray technique at baseline (V0) to assess the status of soft tissue calcifications in the areas of the skin lesions.

5.14Safety Monitoring

Several adverse events, which may occur during the course of the study, are caused by the underlying and often long-lasting disease/condition of calciphylaxis patients.

Adverse events (AEs) will therefore be entered into the eCRF, if they are evaluated as new symptom/medical condition, as AE of special interest (AESI), new diagnosis, changes of laboratory parameters, intercurrent diseases and accidents, recurrence of disease, increase of frequency or intensity of episodical diseases, according to the definition of AEs in section 7.1.1. However, all serious AEs (SAEs) need to be recorded in the eCRF. All patients will be followed for AEs and SAEs for 7 days following the last dose of STS.

Details of assessment and reporting of adverse events are presented in Section 7.

5.15Study Flow Chart

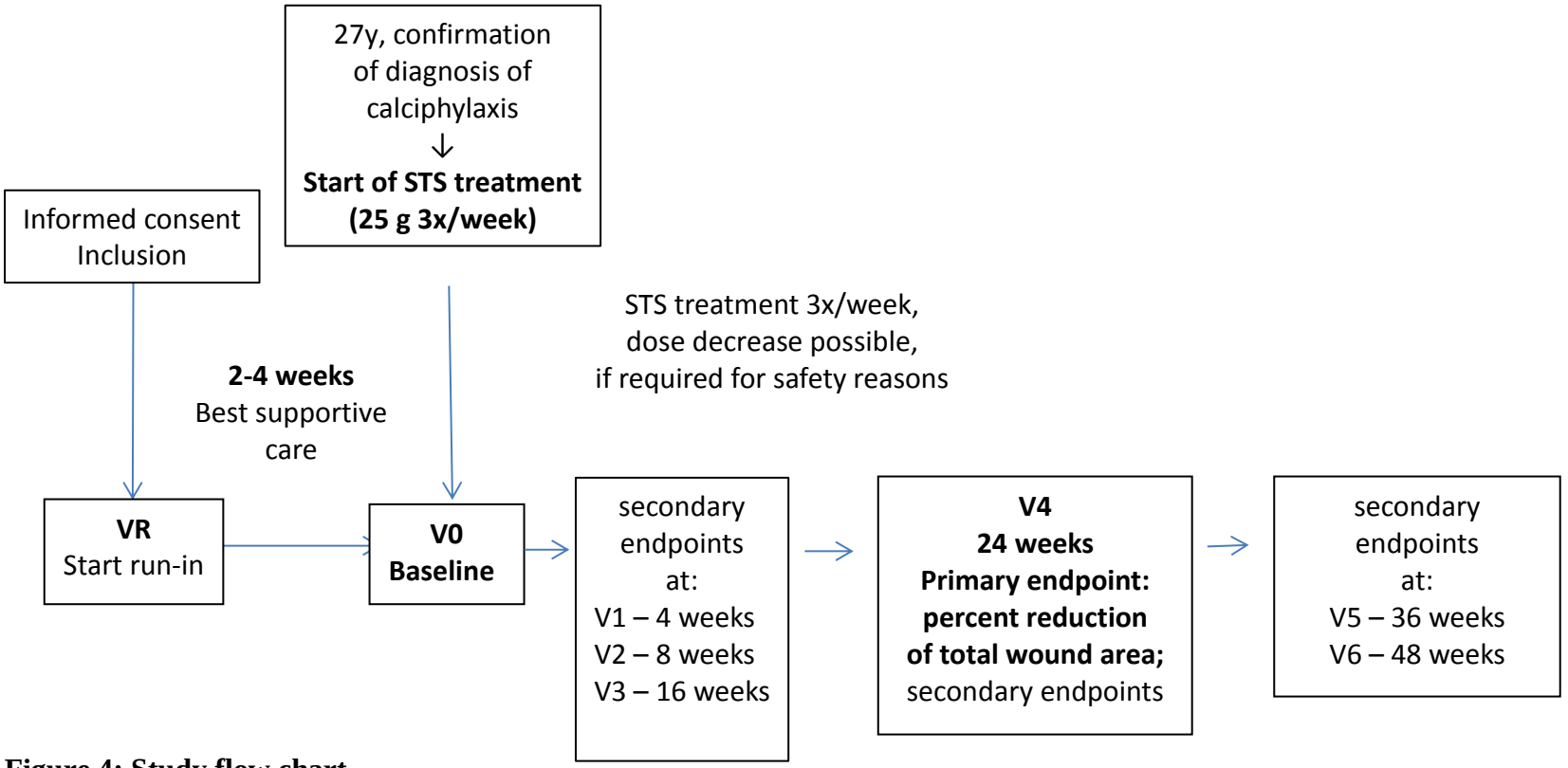

Figure 4: Study flow chart

Table 1: Flow Chart

	Screening	VR Start of run-in phase; duration of 2 to 4 weeks	V0 end of run-in = baseline	V1 4 weeks	V2 8 weeks	V3 16 weeks	V4 24 weeks	V5 36 weeks	V6 48 weeks	SFU 1 0.5 year after treatment	SFU 2 1 year after treatment
Informed consent of the patient	X		X								
Physical examination, vital signs, ECG[1]		X	X	X	X	X	X	X	X		
Inclusion and exclusion criteria,	X		X								
Demographics, baseline characteristics		X									
Skin biopsy for diagnosis of calciphylaxis			X[2]								
Soft tissue radiographs (optional)			(X)								

	Screening	VR Start of run-in phase; duration of 2 to 4 weeks	V0 end of run-in = baseline	V1 4 weeks	V2 8 weeks	V3 16 weeks	V4 24 weeks	V5 36 weeks	V6 48 weeks	SFU 1 0.5 year after treatment	SFU 2 1 year after treatment
Documentation of total wound area (photograph and calculation of wound size)		X	X		X	X	X	X	X		
revPWAT score		X	X		X	X	X	X	X		
Laboratory parameters (including samples for biobanking)		X	X		X	X	X		X		
VAS for pain (0-10)[3]		X	X	X	X	X	X	X	X		
Pain medication requirement		X	X	X	X	X	X	X	X		
Other concomitant medication/measures (e.g. wound debridement)		X	X	X	X	X	X	X	X		
CGI-I				X	X	X	X	X	X		
CGI-S			X	X	X	X	X	X	X		

	Screening	VR Start of run-in phase; duration of 2 to 4 weeks	V0 end of run-in = baseline	V1 4 weeks	V2 8 weeks	V3 16 weeks	V4 24 weeks	V5 36 weeks	V6 48 weeks	SFU 1 0.5 year after treatment	SFU 2 1 year after treatment
Occurrence of new lesions under STS treatment				X	X	X	X	X	X		
BMD (optional)			X						X		
Pregnancy Test		X	X	X	X	X	X	X	X		
Adverse events		X	X	X	X	X	X	X	X		
Survival rate										X	X

[1] ECG only during physical examination at start of run-in phase

[2] If patient is assessed by the investigator as eligible for STS treatment. If a biopsy report of a consisting wound is available at Screening (VR) and the diagnosis of calciphylaxis is confirmed or other causes for necroses and ulcerations were excluded, an additional biopsy is not required.

[3] VAS for pain will be assessed directly before change of wound dressing.

SFU – survival follow-up

6 PLAN FOR TREATMENT OR CARE AFTER THE TRIAL

Patients, who will need further treatment after the end of this clinical trial, will be treated according to current BSC at the respective study site.

Follow-up telephone interviews with the investigators 0.5 and 1 year after the end of the trial are planned (disease status, continuation of STS-treatment, survival, further/additional treatment and new medication for treatment of calciphylaxis).

7 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE may be:

- New symptom/ medical condition,
- New diagnosis,
- Changes of laboratory parameters,
- Intercurrent diseases and accidents,
- Recurrence of disease,
- Increase of frequency or intensity of episodical diseases.

A pre-existing disease or symptom will not be considered an adverse event unless there will be an untoward change in its intensity, frequency or quality. This change will be documented by an investigator.

All AEs (inclusive SAEs) will be documented on an electronic AE-form. AEs are classified as "non-serious" or "serious".

7.1.2 Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) are those events thought to be (potentially) associated with the investigational compound or disease under study. Despite treatment with BSC in the run-in phase or with STS in the study period, calciphylaxis lesions may progress leading to infections, sepsis and potentially to death. Cases were reported where sepsis in

calciphylaxis patients under STS treatment led to death (Norris et al., 2005), (Mataic and Bastani, 2006), (Auriemma et al., 2011). Therefore, infections and sepsis will be assessed as AESIs.

Other AESIs potentially related to STS are the occurrence of metabolic acidosis (Zitt et al., 2013), ventricular tachycardia (Amin et al., 2010), hypotension (Nigwekar et al., 2013), and bone fractures (Adirekkiat et al., 2010). More information about these adverse events is provided in the Investigator's Brochure (IB).

7.1.3 Serious Adverse Event

A serious adverse event (SAE) is one that at any dose (also overdose):

- Results in death,
- Is life-threatening (the term life-threatening refers to an event in which the patient was at risk of death at the time of event and not to an event which hypothetically might have caused death if it was more severe),
- Requires patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/ incapacity,
- Is a congenital anomaly/ birth defect.

All SAE will additionally be documented on an electronic SAE-form.

7.1.4 Expectedness

An 'unexpected' adverse event is one the nature or severity of which is not consistent with the applicable product information, e.g. Investigators Brochure. Furthermore, reports which add significant information on specificity or severity of a known adverse reaction constitute 'unexpected' events.

7.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SAEs that are both suspected, i.e. possibly related to the IMP and 'unexpected', i.e. the nature and/ or severity of which is not consistent with the applicable product information (IB or SmPC) are to be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs).

In case, either the investigator who primary reported the SAE or the second assessor classify the SAE as 'suspected', i.e. related to the IMP and the SAE is 'unexpected' it will be categorized as a SUSAR.

All SUSARs are subject to an expedited reporting to the responsible EC, the competent regulatory authority and to all participating investigators.

7.2 Period of Observation and Documentation

AEs will be documented from a time of the study inclusion up to end of the study up to 48 weeks. All patients who present AEs, whether considered associated with the use of the trial medication or not, will be monitored by the responsible investigator to determine their outcome. The clinical course of the AE will be followed up until resolution/normalization of changed (laboratory) parameter or until it has changed to a stable condition.

Each AE has to be classified in respect to the following five characteristics:

7.2.1 Intensity of the AE

The classification of intensity in this trial will be carried out on the basis of a 3-grade scale as follows:

Mild: signs and symptoms which can be easily tolerated. Symptoms can be ignored or disappear when the patient is distracted.

Moderate: symptoms cause discomfort but are tolerable, they cannot be ignored and affect normal activity.

Severe: symptoms strongly affect normal activity.

7.2.2 Relatedness of the AE to the IMP

The investigator will evaluate each AE that occurred after patient's study inclusion regarding the coherency with the administration of the investigational medicinal product. There will be following criteria for classification in respect to the relatedness to the IMP:

'related': There is a reasonable possibility that the event may have been caused by IMP. A certain event has a **strong temporal relationship** and an

alternative cause is unlikely.

‘probable’: An AE that has a reasonable possibility that the event is likely to have been caused by IMP. The AE has a **timely relationship** and **follows a known pattern of response**, but a potential alternative cause may be present.

‘possible’: An AE that has a reasonable possibility that the event may have been caused by IMP. The AE has a **timely relationship** to the IMP; **however, the pattern of response is untypical**, and an alternative cause seems more likely, or there is significant uncertainty about the cause of the event.

‘unlikely’: Only a remote connection exists between the IMP and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event.

‘not related’: An AE that does not follow a reasonable temporal sequence related to the IMP and is likely to have been produced by the patient’s clinical state, other modes of therapy or other known etiology.

‘not assessable’: The relationship between an AE and the IMP that does not follow a reasonable temporal sequence from trial participation and that is likely to have been produced by the patient’s clinical state, other modes of therapy or other known etiology.

7.2.3 Outcome of the AE

The outcome of an AE at the time of the last observation will be classified as:

‘Recovered/ resolved’:

all signs and symptoms of an AE disappeared without any sequel at the time of the last interrogation,

'Recovering/ resolving':
the intensity of signs and symptoms has been diminishing and/ or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution,

'Not recovered/ not resolved':
signs and symptoms of an AE are mostly unchanged at the time of the last interrogation,

'Recovered/ resolved with sequelae:
actual signs and symptoms of an AE disappeared but there are sequelae related to the AE,

'Fatal': resulting in death. If there are more than one adverse event only the adverse event leading to death (possibly related) will be characterized as 'fatal',

'Unknown': the outcome is unknown or implausible and the information cannot be supplemented or verified.

7.2.4 Action taken with the IMP

The action taken with IMP will be assigned to one of the following categories:

'Dose not changed': no change in the dose of IMP,

'Dose reduced': reduction in the dose of IMP,

'Dose increased': increase in the dose of IMP,

'Drug withdrawn': discontinuation of IMP,

'Unknown': the information is unknown or implausible and it cannot be supplemented or verified,

'Not applicable': the question is implausible (e.g. the patient is dead).

7.2.5 Countermeasures

The term ‘Countermeasures’ refers to the specific actions taken to treat or alleviate adverse events or to avoid their sequelae. Following categories will be used to categorize the countermeasures to adverse events:

‘None’: no action taken,

‘Drug treatment’: newly-prescribed medication or change in dose of a medication,

‘Others’: other countermeasures, e.g. an operative procedure.

7.3 Reporting of Serious Adverse Events by Investigator

All SAEs (including SAEs resulting in death) must be reported by the investigator to the responsible medical monitor of the CRO within 24 hours after the SAE becomes known using the "Serious Adverse Event" form.

Any SAE should be reported to

Name	Assign Safety Desk
Fax	+43 (0) 512 281514 77
Phone	+43 (0) 676 844033835
E-mail	safetydesk@assigndmb.com

The initial report must be as complete as possible including details of the current illness and (serious) adverse event and an assessment of the causal relationship between the event and the trial medication.

In addition, expedited and periodic reporting to regulatory Authorities and IRBs/ECs will be performed in accordance with local requirements. Further reporting details can be found in the study-specific SAE procedure Manual which is in accordance with respective EU requirements, International Conference on harmonization (ICH) GCP, national laws and site-specific requirements.

7.4 Expedited Reporting

SUSARs are to be reported to the EC, competent higher federal authority and to all participating investigators within regulative defined timelines, i.e. they are subject to an expedited reporting.

Investigators participating in this trial will report all SUSARS to Assign Safety Desk as soon as possible but not later than 24 hours after their notification. The reporting will be performed by faxing of a completed 'SAE Form'.

A second assessment and expedited reporting to EC and regulatory authorities will be performed by the sponsor and Assign Safety Desk; details and responsibilities of these pharmacovigilance activities will be defined in a Safety Management plan.

7.5 Emergency Unblinding

not applicable.

7.6 Emergency Treatment

During and following a patient's participation in the trial, the investigator will ensure that adequate medical care is provided to a patient for any AE, if required. The investigator will inform a patient when medical care is needed for intercurrent illness of which the investigator became aware.

8 DATA MANAGEMENT

8.1 Data collection and handling

All protocol-required information collected during the trial must be entered by the investigator, or a designated representative, in the eCRF. Patient data will be coded (see also section 10.3). The investigator, or a designated representative, should complete the eCRF pages as soon as possible after the information is collected, preferably on the same day when a patient is seen for an examination, treatment, or any other trial procedure. Any pending entries must be completed immediately after the final examination. Explanation should be given for all missing data.

The CRO will check completeness, validity and plausibility of data by validating programs, which will generate queries. The investigator or the designated representative is obliged to clarify or explain the queries. The data management is accomplished with the appropriate SOPs valid.

8.2 Electronic Case Report Forms (eCRF)

The case report form represents a faithful reflection of the trial plan requirements.

All data required by the protocol will be carefully and uninterruptedly recorded in the eCRF. eCRF entries and corrections will only be performed by study site staff authorized by the investigator. Each user is informed by the CRO of the clinical study web-site internet address and is allocated to a user account with a personal password to access the confidential web site. The personal password must be kept confidentially and must only be used by the person to whom it was assigned. For additional authorized users at the site, a new user account needs to be requested to ensure that each entry/change can be allocated to the person who performed the entry/change. All visit data need to be recorded in the database as soon as possible after each visit.

Corrections may be requested as follows:

- Investigators' responses are checked as they are entered and are rejected if they do not fulfill quality criteria. A message will specify the type of error and assist in its correction.

- If required, the CRA can ask for information to be corrected during monitoring.
- Computerized data-check programs and manual checks will identify clinical data discrepancies for resolution. Corresponding queries will be created within the system and the site will be informed about new issues to be resolved on-line.

All discrepancies will be solved on-line directly by the investigator or by authorized staff.

8.3 Storage and archiving of data

All important trial documents will be archived by the sponsor for at least 10 years after the trial termination.

The investigator(s) will archive all trial data (source data and Investigator Site File (ISF) including patient identification list and relevant correspondence) according to the section 4.9 of the ICH Consolidated Guideline on GCP (E6) and to local law or regulations.

If a patient withdraws the consent to participate in this study or if the participation will be finished prematurely by the sponsor or the Investigator, the data and samples recorded up to that point will be eligible for study related analysis. All recorded data up to that point will be anonymised after analysis. The Patient will be informed about this procedure in the Inform Consent Form.

9 STUDY MONITORING

9.1 Monitoring

The study will be performed in accordance with Good Clinical Practice and will thus require regular monitoring visits. Monitoring will be done by personal visits from a clinical monitor. Monitoring visits will occur based on patient accruals and availability of entries into the eCRFs. The monitor will review the entries into the eCRFs on the basis of source documents. Details of monitoring (i.e. frequency of visits and/or extent of Source Data Verification (SDV)) will be specified in the monitoring manual for this trial. Between these visits, contacts with study site personnel will be made by telephone, by fax or by mail, to ensure that the trial is conducted according to the protocol and the regulatory requirements.

Prior to the monitor's visit, the investigator will make sure that all data are recorded in the eCRFs. The investigator will allow the monitor access to the "source" data and essential documents and must provide support at all times to the monitor.

During the monitoring visit, the monitor will check with the investigator the progress of the trial and protocol compliance as assessed by the data recorded in the eCRFs. The investigator(s) must agree to permit the monitor to be present to observe the study procedure in one or more patients.

9.2 Source Documents

For each patient included in the study, a specific file (i.e., institution file) must exist with original data, on which is based the information recorded in the eCRF.

Source documents and eCRFs must not be exact copies of each other. As a general rule, medical information that is not specifically required by the study (e.g. patient's sex, prior medical history, prior medication, etc.) must be found in source medical documents (and in the eCRF). Information specifically required by the protocol and not required by routine clinical care may be recorded directly in the eCRF without appearing in source documents. In addition, source documents must mention that the patient has been included in an investigational study. Finally, there must be no data that are inconsistent between eCRF and source documents.

9.3 Inspection / Audits

Regulatory authorities or an auditor authorized by the sponsor may request access to all source documents, eCRF, and other trial documentation. Direct access to these documents must be guaranteed by the investigator who must provide support at all times for these activities. Patients will be generally informed about this opportunity during informed consent procedure.

For Switzerland only: The Ethic committee also may request access to all source documents and trial documentations. The Access to these data must be guaranteed by the investigator.

10 ETHICAL AND LEGAL ASPECTS

10.1Good clinical practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by Good Clinical Practice (GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

10.2 Patient information and informed consent

Before being admitted to the clinical trial, the patient must consent to participate after the nature, scope, and possible consequences of the clinical trial have been explained in a form understandable to him or her. The patient must give consent in writing. The signed Informed Consent Form will be filed by the investigator.

A copy of the signed informed consent document must be given to the patient. The documents must be in a language understandable to the patient and must specify who informed the patient.

The patients will be informed as soon as possible if new information may influence his/her decision to participate in the trial. The communication of this information should be documented.

10.3 Confidentiality

The data obtained in the course of the trial will be treated pursuant to the Federal Data Protection Law.

During the clinical trial, patients will be identified solely by an individual identification code (country number, site number, patient number). The patient date of birth will not used for the identification. Trial findings stored on a computer will be stored in accordance with local data protection law and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation will be fulfilled in its entirety.

The patient consents in writing to release the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by the EC, the competent regulatory authorities and authorized persons (inspectors, monitors, auditors). Authorized persons (clinical monitors, auditors, and inspectors) may inspect the patient-related data collected during the trial ensuring the data protection law.

The investigator will maintain a patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

Patients who did not consent to circulate their coded data will not be included into the trial.

10.4 Responsibilities of investigator

The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the trial treatments, and their trial-related duties and functions.

The investigator should maintain a list of Sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

10.5 Approval of trial protocol and amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent EC as well as to the competent regulatory authority. A written favorable vote of the EC and an (implicit) approval by the

competent regulatory authority are a prerequisite for initiation of this clinical trial. The statement of EC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member. This documentation must also include a list of members of the EC present on the applicable EC meeting and a GCP compliance statement.

Before the first patient is enrolled in the trial, all ethical and legal requirements must be met. All planned substantial changes will be submitted to EC and the regulatory authority in writing as protocol amendments. They have to be approved by the EC and the regulatory authority.

The investigator and the CRO will keep a record of all communication with the EC and the regulatory authorities.

10.6 Continuous information to independent ethics committee

Persuant to GCP Ordinance, the EC and the regulatory authority will be informed of all suspected serious unexpected adverse reactions (SUSARs), SAEs resulting in death and all AEs resulting in death or being live-threatening occurring during the trial. Both institutions will be informed in case the risk/ benefit assessment did change or any others new and significant hazards for patients' safety or welfare did occur. Furthermore, a report on all observed serious adverse events (SAEs) will be submitted once a year – Developmental Safety Update Report (DSUR).

The EC and the regulatory authorities must be informed of the end of the trial. They will be provided with a summary of trial results within one year after the end of clinical phase (LPO).

10.7 Notification to regulatory authorities

The local regulatory authorities responsible for each particular investigator will be informed before the beginning, during and at the end of the trial according to the applicable regulations. Each investigator is obliged to notify his/ her local regulatory authority. This responsibility has been delegated to the CRO.

10.8 Registration of the trial

Prior to the beginning of the clinical phase (FPI), the CRO will register the trial at Current Controlled Trials (https://www.clinicaltrialsregister.eu/index.html, http://www.controlled-trials.com or http://www.clinicaltrials.gov). Thus the trial will be given a unique ISRCTN, which is a prerequisite for a publication in a peer-reviewed medical journal.

10.9 Insurance

For patients enrolled in this clinical trial, the sponsor will contract a patient insurance.

The name, address and the insurance policy number will be given to both the investigator and to each study subject prior to enrollment. Moreover a copy of the insurance conditions will be filed on site. The Patient will be informed in the Inform Consent Form about the procedures in case of any potential violations and will be instructed to contact the Principle Investigator or the Insurance Company directly. The contact details from the insurance company are also provided in the Patient Inform Consent Form.

Any impairment of health which might occur in consequence of trial participation must be notified to the insurance company. The patient is responsible for notification. The insured person will agree with all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.

During the conduct of the trial, the patient must not undergo other clinical treatment except for cases of emergency. The patient is bound to inform the investigator immediately about any adverse events and additionally drugs taken. The terms and conditions of the insurance should be delivered to the patient.

The insurance company has to be informed about all amendments that could affect the patient’s safety.

11 STATISTICAL METHODS

11.1 Methods of Statistical Analysis

Statistical methods will be described in detail in the Statistical Analysis Plan (SAP).

The trial objectives will be evaluated by statistical hypothesis testing, summary tables and figures and by data listings.

All analyses will be performed using SAS® Version 9.2 or later and SAS JMP Version

10 or later.

11.2 Analysis Sets

11.2.1 Progressors and Non-Progressors

There will be two patient groups, both receiving the same treatment medication, which will be analysed separately. Depending on whether the disease is rapidly progressing during the run-in phase, patients are either assigned to the progressor (Group A) or the non-progressor group (Group B) at the time of enrolment. The main efficacy analysis will solely be based on the progressor group while the safety analysis will be based on the pooled data from progressors and non-progressors. Additional analyses will be performed on progressors and non-progressors individually and on the pooled set. These analyses are considered as supportive.

Safety Set The safety set consists of all enrolled patients for whom infusion of study medication had been started. All safety analyses will be performed on the safety set.

11.2.2 Full Analysis Sets (FAS)

The FAS sets for progressors (Group A) and non-progressors (Group B) consist of all patients in the corresponding group for whom infusion of study medication had been started, and for whom at least one post baseline measurement of the total wound area will be available. Even though it is expected, that there will be a significant number of drop-outs, most of these drop-outs will likely occur at a later stage of the treatment, i.e. after V1 (see 11.2.4). The FAS datasets as defined here should therefore include almost all enrolled patients.

All efficacy analyses will be performed primarily on the FAS subset of the progressors group, i.e. Group A.

11.2.3 Per Protocol Set (PPS)

The PPS sets consist of all randomized patients in the corresponding group included in the FAS, but will exclude the following:

- patients violating major inclusion/exclusion criteria related to efficacy;
- patients deviating from the protocol in an extent that causes bias for efficacy evaluation (e.g. no 24-week efficacy data available);
- patients with severe disease status which may be switched to STS treatment earlier than 2 weeks.

The final exclusion of patients from the PPS will be done at the blind review meeting on an individual patient basis.

All relevant efficacy analyses will also be conducted on the PPS. These analyses are considered as supportive for the analyses performed on FAS.

11.2.4 Missing value treatment

There is a variety of possible reasons for missing values, mostly due to the very aggressive nature of the disease, the generally very bad health state of the patients and their low life expectancy. Drop-outs due to severe treatment side effects are by contrast rather unlikely, partly because STS is generally well tolerated, partly because dose reduction is a possible alternative to a complete stop of treatment.

Nevertheless, the possibly incomplete list of drop-out reasons includes nausea, extreme pain, infections, the complete stop of treatment, transplantation, or patient's death. Apart from nausea, all other reasons are likely not treatment related. It is also expected, that drop-outs will occur with an approximately constant rate. Therefore, at least V1 data should be available for most patients.

Due to the longitudinal assessment schedule of the efficacy parameters, the use of a pattern mixture model for missing value treatment will likely provide better results than the use of the Last Observation Carried Forward (LOCF) method or other simple approaches. Details will be given in the SAP.

11.3 Baseline

Baseline measurements of the relevant efficacy and safety variables will be taken after enrolment of the patient for starting of STS treatment. Change from baseline will be calculated as the difference in post-baseline versus baseline values. Selected pre-baseline measurements (from start of the run-in phase) will be analyzed exploratively.

11.4 Descriptive Statistics

Categorical data will be summarized by means of absolute and relative frequencies (counts and percentages). Continuous data will be summarized by means of the following summary statistics: number of observations, arithmetic mean, standard deviation, minimum, median, maximum and quartiles.

Where appropriate, data will be visualized by means of box-whisker plots, arithmetic mean courses over time or Kaplan-Meier Plots for censored data.

11.5 Analysis of Efficacy

The main statistical analysis of the primary efficacy variable will be performed on the FAS of the progressors group (Group A) using the missing value handling approach as described in 11.2.4 Additional analyses on the PPS will be considered as supportive. If no efficacy data has been recorded before death and cause of death will be clearly unrelated to the treatment, the patient will be removed from the analysis.

11.5.1 Primary Efficacy Analysis

Change in total wound area until between baseline and V4 (24 weeks after start of medication) will be analyzed as the primary efficacy variable. At V0 and V4 photographs of all wounds are taken according to the description in section 5.2. The size in square centimeters of each individual wound will be assessed by two independent and blinded dermatologists using appropriate image analysis software and the means of both assessments will be calculated for each time point. The dermatologists will neither know at what time point images were taken nor will they know that two sets of images show the same patient at a different time point.

The mean area of each wound of a given patient at a given time point will then be summed up over all wounds and used to calculate the percent change in wound size.

As stated before, calciphylaxis is a highly progressive disease with rapidly deteriorating skin lesions. Without treatment or treated with standard medication, a clear worsening of lesions between V0 and V4 would take place. On the other hand, based on literature data and information from physicians, a decrease in wound size of 20% or more under STS treatment can clearly be considered as clinically relevant, because wound size is correlated with the detrimental symptoms of calciphylaxis and such a decrease in wound size would be a notable improvement for patient condition.

The change in total wound area will be analyzed using a One-sample Wilcoxon Signed Rank test. The sample median together with the corresponding confidence interval will also be given.

11.5.2 Secondary Efficacy Analysis

Pain reduction and the consumption of pain medication after 4, 8, 16, 24, 36 and 48 weeks compared to baseline will both be treated as continuous variables and independently analyzed using One-sample Wilcoxon Signed Rank Tests with a pattern mixture model approach for missing data.

Untreated pain level and/or the consumption of pain medication will significantly increase over time as the disease progresses. Any significant decrease in either parameter is a strong signal for a positive treatment effect. Even though there is supposedly a strong negative correlation between the two parameters, they will be analyzed individually at an alpha level of 0.025 one sided. Additionally, for every patient, pain level and medication consumption will be plotted as a time course covering all visits from VR to V6.

Bone mineral density (BMD) will be tabulated and analyzed descriptively.

Patient survival will be tabulated descriptively and visualized using a Kaplan Meier plot. Additionally, the overall survival after start of STS treatment and the one-year survival rate will be explicitely stated.

The assessment of total wound area, skin lesions using the revPWAT score and the clinical global impression using the CGI-S scale and CGI-I score will be tabulated descriptively and plotted as a time-course using box-whisker plots.

Patients with total remission of the wound area will be listed with the corresponding time after beginning of STS treatment. The fraction of patients with total wound remission, and for these patients, descriptive statistics about time to remission will also be provided.

Accordingly, the use of wound debridement and change in the eligibility of patients for kidney transplantation will also be analyzed

11.6 Analysis of Safety

Safety and tolerability will be assessed in terms of AEs and vital signs, and laboratory parameters will be determined using the safety analysis set. The number of AEs, which are reported in addition to the symptom complexes considered as AEs from the underlying disease, and the number and percentage of patients reporting at least one AE will be summarized by system organ class (SOC), preferred term (PT), treatment group and overall. When counting patients, an AE reported more than once will be counted only once but with its highest degree of severity. An AE will be considered treatment-emergent (TEAE), if it occurs for the first time, or worsens in terms of seriousness or severity. Summaries of treatment-emergent serious AEs, AEs leading to withdrawal, AESIs and AEs by severity and relationship to study medication will be presented.

No statistical hypothesis testing is intended on safety and tolerability data.

11.7 Laboratory Parameters

All laboratory data will be analyzed using descriptive statistics. Additionally, the number of patients with laboratory values below, within and above normal range will be determined for each parameter and time point.

11.8 Sample Size Estimation

11.8.1 Calculation procedure

There is no straightforward sample size calculation possible for this study. Firstly, neither reliable estimates for the effect size nor for the variability of the treatment effect are known, secondly, a relatively high drop-out rate is expected based on data from the literature. Sample size is therefore chosen both based on rough estimates of effect size and variability and on feasibility considerations, the latter mainly effected by the low incidence of calciphylaxis. Another issue which needs to be considered is the fact that only patients with progressing calciphylaxis will be assigned to the efficacy analysis group (Group A). However it is expected, that the number of non-progressors will be very small.

Sample size calculation for the confirmatory efficacy parameter is performed using version 3.17 of the G*Power application. Power is set to 80%, maximum alpha error to 0.05 two sided corresponding to 0.025 one-sided.

11.8.2 Reduction in total wound area

Percent reduction in total wound area will be analyzed as the primary efficacy variable. A median reduction of at least 50%, significantly higher than the 20% reduction which are already considered as clinically relevant are expected for this parameter. The standard deviation for this parameter should be no higher than approximately 100%: This results in a standardized effect size (Cohen's d) of about 0.6 and a sample size of about 25 patients. This number needs to be increased for two reasons. Firstly, only patients which show progressing disease status during the run-in phase will be included in the efficacy analysis group and secondly, there is a relatively high risk of drop-outs. In a calciphylaxis study (clinicaltrials.gov identifier: NCT00568399), only 60% of the study participants actually completed the study. For the current study, patients will be analyzed if at least one post recruitment score will be available. This should be the case for the majority of the patients. Nevertheless to account for the reasons mentioned above, the sample size will be increased by 50% and a total sample size of 40 patients will be used.

This number should provide good estimates with small enough confidence intervals for both the primary and possibly also for one or more of the secondary efficacy parameters.

12 AGREEMENTS

12.1 Financing of the Clincial Trial

The clinical trial will be financed by Dr. F. Köhler Chemie GmbH.

12.2 Financial Disclosure

Before the start of the trial, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the sponsors, in the investigational product or any commercial organisation being involved in the clinical trial. The investigator has also to confirm that he/she has not entered into any financial arrangement, whereby the value of compensation paid could affect the outcome of the clinical trial.

The investigator agrees to update this information in case of significant changes.

12.3 Reports

The *CRO* will prepare the integrated report according to ICH E3, in agreement with the sponsor.

12.4 Publication

The results will be published, preferably in a Nephrological or General Medicine Journal. All information concerning the trial is confidential before publication. Paying due regard to statutory rights and duties of a university, the investigators shall be entitled to publish, in consultation with the sponsor and after completion of the research work, the scientific findings for scientific purpose. A manuscript of the intended publication must be submitted to the sponsor (Dr. F. Köhler Chemie GmbH) for scrutiny at the latest 60 days prior to publication. Proposals for changes and modifications submitted by the sponsor ought to be taken into consideration, unless said proposals interfere with the scientific nature or the neutrality of the publication. A publication of the results in an international peer-reviewed journal is planned at the end of study.

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DR. F. KÖHLER CHEMIE

EudraCT-Nr. 2014-002128-28

Declaration of Consent

The clinical trial STS-CSM-1/13 will be conducted in accordance with the EU recommendations on "Good Clinical Practice (GCP)". It is certified that the trial plan, the documentation file and the appendices all contain the items of information and decisions necessary for the conduct of the study, and the study will be carried out and documented in accordance with this trial plan and that the legislative provisions and the agreements described will be adhered to.

Signature list:

Name	Function	Date	Signature
Dr. Roman Petrov Dr. F. Köhler Chemie GmbH	Sponsor	29.05.17	
Dr. Anton Klingler Assign Data Management and Biostatistics GmbH	Biostatistician		

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Dr. Anton Klingler Assign Data Management and Biostatistics GmbH	Biostatistician	29-Aug-2017	

A Prospective Multicenter Phase 2/3 Clinical Trial with Sodium Thiosulfate for the Treatment of Calciphylaxis

PROTOCOL Nr. STS-CSM-1/13

Version 4.2, 02.02.2017

EudraCT-Nr. 2014-002128-28

Sponsor:

Dr. F. Köhler Chemie GmbH

Dr. Gernot Köhler
Werner-von-Siemens-Str. 14 - 28
D-64625 Bensheim
Germany
Phone: +49-6251-1083-0
Fax: +49-6251-1083-146

Statistician:

Dr. Anton Klingler
Chief Executive Officer
Assign Data Management and Biostatistics GmbH
Stadlweg 23
6020 Innsbruck
Austria
Ph: +43 512 890 064 121
Fax: +43 512 281 514

Monitoring:

Celerion Clinical Research GmbH
Hainburger Strasse 33
1030 Vienna
Austria
Phone: +43 1 40 33 805 0
Fax: +43 1 403 38 05 66

SYNOPSIS

Title	**A prospective multicenter Phase 2/3 study with sodium thiosulfate for the treatment of calciphylaxis**
Study Rationale	Up to now, no prospective clinical trial with STS has been performed. Reasons are that calciphylaxis is a rare condition and treatment is not focused on certain centres. The previous case reports on successful treatments of calciphylaxis patients with STS support the intention to demonstrate the efficacy and safety of STS in this patient population under the conditions of a prospectively planned clinical trial.
Clinical Phase	2/3
Indication	Treatment of calciphylaxis
Objectives	- The objective of this project is to study the potentially beneficial effects of sodium thiosulfate (STS) on the course and outcome of calciphylaxis. - A run-in phase of 2 to 4 weeks will be established, during which patients will be treated with conventional medications and measures. If the investigator observes typical symptoms of calciphylaxis (pain, appearance of more than one wound lesion) and decides that the patient is eligible for the treatment with STS and participation in the clinical trial, a biopsy will be taken to confirm the diagnosis of calciphylaxis by excluding other causes of skin necroses and ulcerations. If a biopsy report of a consisting wound is available at Screening (VR) and the diagnosis of calciphylaxis is confirmed or other causes for necroses and ulcerations were excluded, an additional biopsy is not required. - Patients with rapidly progressive disease under BSC will be allocated to Group A while patients with less progressive or initially stable disease will be allocated to Group B. Patients of both groups will be treated with STS. Both patients groups will be analysed separately, with the former to establish efficacy and the latter to be assessed descriptively. It is expected, that by far the majority of patients will be in the progressor group. - The run-in phase will end on the same day, when patients will start treatment with STS (baseline, V0). - Follow-up visits will be performed after 4 (V1) 8 (V2), 16 (V3), 24 (V4), 36 (V5) and 48 weeks (V6) after start of STS treatment. **Primary Endpoint:** Percent reduction of the total wound area after 24 weeks (V4) compared to baseline (V0) as assessed by 2 independent, blinded dermatologists using a serial photo documentation. The mean value of both assessments will be taken. **Secondary Endpoints**:

	Status of skin lesions: - Total wound area at 8, 16, 36, 48 weeks compared to baseline (V0). - Complete remission of wound area. - Qualitative improvement of skin lesions at 8, 16, 24, 36, 48 weeks as assessed by the revised Photographic Wound Assessment Tool (revPWAT) score and evaluation of a serial photo documentation through 2 independent, blinded dermatologists. - Use of wound debridement Pain: - Reduction of pain in the areas of calciphylaxis after 4, 8, 16, 24, 36 and 48 weeks after start of STS treatment will be compared to baseline (V0) and assessed by a visual analogue scale (VAS) for pain (0-10). This will be done directly before changing the wound dressing. - Consumption of pain medication (normalized to morphine equivalent with an appropriate conversion table) will be assessed at VR, V0 and 4, 8, 16, 24, 36 and 48 weeks after start of STS treatment and compared to baseline (V0). Clinical global impression: - Change in clinical global impression as assessed by the Clinical Global Impressions-Improvement (CGI-I) score at each follow-up visit (after 4, 8, 16, 24, 36 and 48 weeks) compared to baseline (V0) and the Clinical Global Impression-Severity scale (CGI-S) through the investigators. The Clinical Global Impression-Severity scale (CGI-S) will be assessed at each visit from visit V0 to V6 (i.e. after 4, 8, 16, 24, 36 and 48 weeks). Improvement leading to eligibility of the patient for kidney transplantation - Eligibility for kidney transplantation is given when the patient is being actively listed on a transplant waiting list. Occurrence of new lesions: - Time point of occurrence and – if applicable – healing as well as location of each lesion to be documented at each visit (V0 to V6) Bone mineral density (BMD) - Bone scans by Dual Energy X-ray absorptiometry (DEXA) technique at baseline and after 48 weeks (V6)

	Survival: - Median overall survival after start of STS treatment - One-year survival rate **Safety parameters:** - Adverse events - Adverse events of special interest (AESI; incidence of infections and sepsis, metabolic acidosis, ventricular tachycardia, hypotension, bone fractures). - Use of other concomitant medications - Physical examinations, ECGs, vital signs (heart rate, blood pressure) - Tolerability of STS treatment Laboratory parameters (PTH, total calcium, phosphorus, alkaline phosphatase, pH, CRP, leucocytes, hemoglobin, creatinine, albumin), **Biobanking:** - collection of serum for assessing further relevant parameters, e.g. inflammatory and calcification parameters and bone turn-over markers - T50 test (in vitro blood test for calcification propensity by monitoring the maturation time (T50) of calciprotein particles in serum.
Study design	The study design is a prospective, open, uncontrolled multicenter, Phase 2/3 clinical trial including various dialysis centers in Europe Each patient will serve as his/her own control. A median reduction of at least 50% in total wound area at V4 compared to V0 is expected for patients treated with STS. This is far above the 20% wound reduction which is already considered as clinically relevant. Patients with suspected calciphylaxis will be asked if they agree to participate in the clinical trial and to undergo STS treatment, after conventional medications and measures given during the run-in phase of 2 to 4 weeks were assessed by the investigator as insufficiently or not at all effective. The study duration for each patient will be up to 48 weeks after start of STS treatment. Patients, who will need further treatment after the end of this clinical trial, will be treated according to current BSC at the respective study site.

	At 0.5 and 1 year after the end of the clinical trial, the investigators will be contacted again and asked about the disease status, continuation of STS treatment and survival of the patients, further/additional treatment and new medication for treatment of calciphylaxis.
Number of Subjects	The study population will consist of 40 dialysis patients diagnosed with calciphylaxis.
Duration of Study	The duration of participation for each patient will be up to 48 weeks plus 2 to 4 weeks run-in phase. The overall duration of the trial is expected to be approximately 4 years.
Inclusion Criteria	(1) All patients ≥ 18 years (2) Male or female hemodialysis (HD) patients with a diagnosis of calciphylaxis. (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching). (3) Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study
Exclusion Criteria	(1) Sodium metabisulfite hypersensitivity, among others the history of bronchial asthma due to known sodium metabisulfite hypersensitivity (2) Females who are pregnant (positive pregnancy test at screening or during study phase) or lactating. If having reproductive potential are considered potentially ineligible with respect to use highly effective methods of birth control throughout the study. (3) Patients who have participated in any other investigational studies within 30 days previous to enrollment (4) History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment. (5) Good response to conventional treatment. (6) Life expectancy less than 4 months in the judgment of the investigator
Treatments	At start of the run-in phase (VR) of 2 to 4 weeks, patients will be treated with conventional medications and measures. If the investigators assess the patients as eligible for the treatment with STS and for participating in the clinical trial, a biopsy will be taken during the run-in phase to confirm the diagnosis of calciphylaxis by excluding other causes of necroses and ulcerations.

	At the end of the run-in phase, i.e. the day defined as baseline (V0), patients will be treated with STS for at least 24 weeks. The starting dose will be 25 g per day given 3x per week 30 min before end of HD over an infusion period of 60 min. In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms. In case of complete remission of the wound lesion after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4) the dose may only be reduced for safety reasons. Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed.
Safety Parameters	Safety assessments start at the time point, when the patient enters the run-in phase (VR). If the patient is excluded from the trial at baseline (V0) because the diagnosis of calciphylaxis cannot be confirmed, other eligibility criteria are not met or because the patient withdraws the consent for STS treatment, the patient will not be followed up in the trial beyond that time point for further assessments of safety parameters.
Sample Size Determination	Based on published data, a very strong effect on the primary efficacy variable with a standardized effect size (Cohen‘s d) of at least 0.6 is expected, corresponding e.g. to a median reduction in wound area of 60% with a standard deviation of 100%. A sample size of 25 patients will have 80% power to detect a significant result with a 0.025 one-sided significance level under these assumptions. Given a possibly high drop-out rate and also some non-progressing patients which will not be assigned to the efficacy analysis group, a total number of 40 patients will be recruited.
Statistical Analysis	The main statistical analysis of the primary and secondary efficacy parameters will be performed on the FAS using a pattern mixture model approach for missing data. As there will be no control group, optimistic assumptions about disease development for untreated patients will be used for the efficacy analysis. The primary efficacy variable percent reduction in the total wound

	area until V (24 weeks) will be analyzed with a One-sample Wilcoxon signed rank test.

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LIST OF ABBREVIATIONS

ALAT	Alanine Transferase
AP	Alkaline Phosphatase
ASAT	Aspartate Transferase
BSC	Best Supportive Care
CGI-I	Clinical Global Impressions-Improvement score
CGI-S	Clinical Global Impression-Severity scale
CKD	Chronic Kidney Disease
CRP	C-reactive protein
CTx	turn-over marker for bone resorption
CUA	Calcific Uremic Arteriolopathy
COMP	Committee of Orphan Medicinal Products
EC	Ethics Committee
eCRF	electronic Case Report Form
EMA	European Medicines Agency
ESRD	End Stage Renal Disease
ETHE1	Ethylmalonic Encephalopathy 1
FAS	Full Analysis Set
FFP	Fresh Frozen Plasma
GGT	Gamma-glutamyltransferase
HD	Hemodialysis
LOCF	Last Observation Carried Forward

MGP	Matrix GLA protein
pO_2	Oxygen Partial Pressure
PPS	Per-Protocol Set
PSUR	Periodic Safety Update Report
PTH	Parathyroid Hormone
pVO_2	Venous Oxygen Tension
SAP	Statistical Analysis Plan
SB	Standard Bicarbonate
SFU	Survival Follow Up
sO_2	Venous Oxygen Saturation of Hemoglobin
SQR	Sulfur-Quinone Oxidoreductase
STS	Sodium Thiosulfate
TS	Thiosulfate
TST	Thiosulfate Sulfurtransferase (= Rhodanese)
VAS	Visual Analogue Scale

1 INTRODUCTION AND BACKGROUND

1.1 Information on Calciphylaxis

Calciphylaxis, also known as calcific uremic arteriolopathy (CUA), is a rare but catastrophic disease which mainly affects patients with end stage renal disease (ESRD) and is associated with a 1-year mortality of 60-80% of the patients (Wilmer and Magro, 2002; Weenig, 2008; Schlieper et al., 2009; Rogers and Coates, 2010). Calciphylaxis is histologically characterized by the triad of calcification of the media, proliferation of the intima, and thrombosis of the lumen of small skin vessels. Clinically, these changes lead to progressive and very painful non-healing ischemic skin ulcerations typically at the lower extremities and/or the abdomen. Assuming an annual incidence of 1-2% among dialysis patients (Musso et al., 2009), (Fine and Zacharias, 2002), (Angelis et al., 1997), e.g. in Switzerland, an estimated 15 to 25 new cases of calciphylaxis are currently expected to occur per year.

Unfortunately, to date there are neither proven therapies available for calciphylaxis, nor is there an established animal model to study its pathophysiology and to test potential treatment modalities. Clinical factors often associated with calciphylaxis include ESRD, female gender, hyper- or hypoparathyroidism, obesity, hyperphosphatemia, hypercalcemia, and the use of vitamin K antagonists (Schlieper et al., 2009).

With the current pathophysiologic concept of heterogenous and ill-defined derangements of mineral metabolism, treatment is aimed at arresting the proposed driving forces of calcification of the medial layer of the small skin arterioles in the hope to stop or reverse disease progression.

1.2 Pathophysiology of calciphylaxis

The development of calciphylaxis can be considered a two-step process: the development of the vascular lesion and the development of tissue ischemia due to the vascular lesion, plus other clinical events (Hanke et al., 2010), as demonstrated in Figure 1.

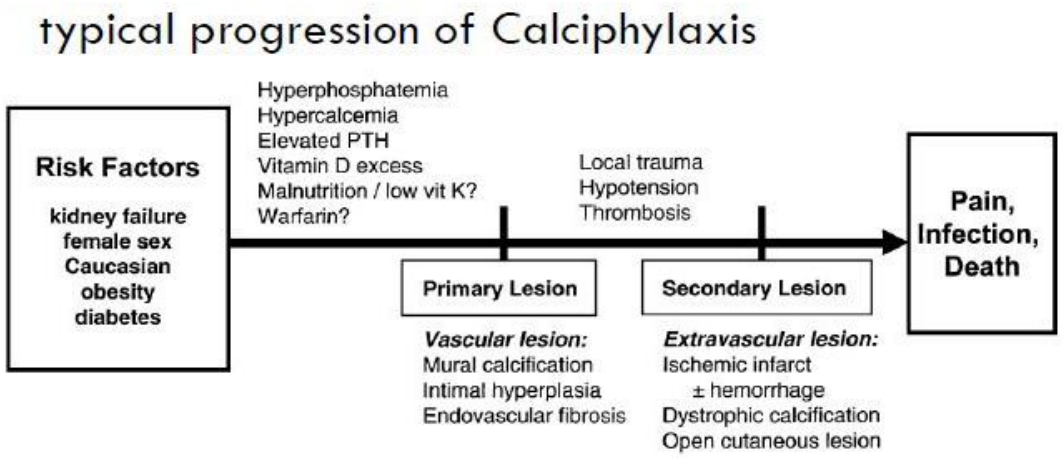

Figure 1: Development of calciphylaxis organ damage

Calciphylaxis affects skin arterioles in the subcutaneous tissue and leads to ischemic skin necroses, often clinically accompanied by opioid-resistant pain and non-healing ulcerations. Histologically, the skin lesions are characterized by medial calcification, endothelial proliferation and luminal thrombosis and are accompanied by a dramatic impairment of skin nutrition and ensuing skin (Brandenburg et al., 2011).

The order of occurrence of the histologic lesions and their potential role in the pathogenesis of calciphylaxis has not been clarified yet. Whereas it seems prudent to assume that the thrombotic occlusion of the vessel lumen is the final step in a cascade of events, it is not clear whether endothelial proliferation and medial calcification do occur concomitantly or sequentially, and if the latter was true – which comes first.

1.3 Conventional treatment options for calciphylaxis patients

Calciphylaxis patients represent by nature a very heterogeneous population with a broad range of calciphylaxis- associated and non-associated medications and diagnoses (as an estimate, the average dialysis patient has 10-15 diagnoses and is on 10-15 different drugs). No standard treatment options for calciphylaxis patients are available.

Treatment modalities, which have been tested so far, are highly variable and all without decisive improvements of the disease course. Amongst others, treatments comprise the cessation of vitamin K antagonists, calcium containing phosphate binders and vitamin D compounds, the lowering of serum phosphate and calcium levels, the use of calcimimetics and of bisphosphonates (Smith et al., 2012), (Veitch et al., 2014). Furthermore, intensified dialysis, meticulous wound care and skin grafting, and even parathyroidectomy have been tried but have not been shown to be convincingly effective (Weenig et al., 2007). The only treatment modality, which was related more constantly with improved pain and wound healing, is the application of hyperbaric oxygen treatment (Benedetto and Emhoff, 2000), (Dean and Werman, 1998) (Benedetto and Emhoff, 2000), which is, however, available in selected centers only.

Apart from these measures, treatment is mainly symptomatic with intensified wound care, and the liberal use of antibiotics and analgesics. Unfortunately, none of these measures alone or in combination has convincingly changed the course and prognosis of calciphylaxis.

1.4 Sodium thiosulfate (STS) for the treatment of calciphylaxis

Sodium Thiosulfate (STS, $Na_2S_2O_3$) is a sulfur salt, which has been used for decades in human medicine and was approved for (i) the treatment of cyanide intoxications (Miller and Toops, 1951) and (ii) as a chemoprotectant against cisplatin-induced oto- and nephrotoxicity (Gandara et al., 1990).

Besides these indications, STS has anecdotally been reported to prevent the progression of nephrocalcinosis (Agroyannis et al., 2001), metastatic calcifications (Papadakis et al., 1996), (Yatzidis, 1985), (Yatzidis and Agroyannis, 1987), kidney stones (Yatzidis, 1985), and coronary artery calcification (Adirekkiat et al., 2010).

In addition, based on theoretical considerations STS has been first used for the treatment of calciphylaxis back in 2004 (Cicone et al., 2004). Case reports in more than 280 patients are available indicating that STS might be beneficial for the treatment of calciphylaxis both in improving the severe pain associated with the condition and in the healing of calciphylaxis lesions (Guerra et al., 2005), (Landau et al., 2007), (Mataic and Bastani, 2006), (Ackermann et al., 2007), (Zitt et al., 2013). Since then, STS has been used off-label for treatment of calciphylaxis but has also been investigated in open label, clinical studies for treatment of other calcifications (e.g. (Adirekkiat et al., 2010).

On 23 February 2011, orphan designation (EU/3/10/848) was granted by the European Medicines Agency (EMA) for sodium thiosulfate for the treatment of calciphylaxis (EMA-COMP, 2011).

The literature documenting the use of STS in the treatment of calciphylaxis is comprehensively reviewed by *Smith et al.*, along with a detailed summary of case reports and case series. Most of these reports documented treatment success, with rapid resolution of pain within days or weeks, often supported by impressive reductions in requirements for analgesia. Cessation of new lesion formation along with complete or partial wound healing or reduction in the size of subcutaneous plaques was also commonly reported. However, most reports described single cases or retrospective analyses of a small number of patients at dialysis centers (Smith et al., 2012), (Zitt et al., 2013), (Salmhofer et al., 2013).

Recently, a retrospective data collection on 172 calciphylaxis patients in centers in the USA over a period of 4 years was reported (Nigwekar et al., 2013). Of these, a complete survey was available for 53 calciphylaxis patients demonstrating substantial improvement in their symptoms. Among surveyed patients, calciphylaxis completely resolved in 26.4%, markedly improved in 18.9%, improved in 28.3%, and did not improve in 5.7% of the patients; in the remaining patients (20.8%), the response was unknown. One-year mortality in patients treated with STS was 35% compared to 60-80% without treatment (Weenig et al., 2007).

1.5 Mode of action of STS

The mode of action of STS is still not completely clarified, however, there are hypothetical models explaining the action of STS in vascular calcification in general, which may be extrapolated to its action in calciphylaxis.

STS appears to have pleiotropic pharmacodynamic properties which might explain its beneficial effects in the diverse spectrum of clinical applications mentioned above. When applied as an antidote in cases of cyanide intoxications, thiosulfate and cyanide are converted to the less toxic thiocyanate by the action of the mitochondrial enzyme thiosulfate sulfurtransferase (TST = rhodanese) (Hildebrandt and Grieshaber, 2008). In contrast, the detoxification of the chemotherapeutic cisplatin is accomplished by the formation of a thiosulfate-cisplatin complex, which prevents the entry of cisplatin into cells and probably facilitates its excretion from the body.

The calcification preventing and anti-ischemic properties of STS, which are probably effective in the treatment of calciphylaxis, may in contrast be due to the following mechanisms of action: (i) chelation/solubilization of calcium (O'Neill, 2008), (ii) induction of an anion gap acidosis (Cicone et al., 2004), (iii) anti-oxidative properties (Hayden and Goldsmith, 2010) (8), (iv) upregulation of calcification preventing proteins (e.g. Matrix GLA Protein [MGP] and fetuin-A) (Pasch et al., 2008), and (v) generation of H_2S, a potent vasodilator (Sen et al., 2008), (Hayden et al., 2008).

Hayden et al. 2005 have formed a hypothesis that the rapid reduction in pain may be due to a restoration of endothelial function associated with this syndrome. The antioxidant effect of STS, given in the i.v. dosing of 12.5–25 grams i.v. at the end of dialysis may help to restore the dysfunctional endothelial cell and begin restoring the endothelium's natural tendency (in health) to produce endothelial nitric oxide (eNO) promoting vasodilation instead of the damaging super oxide and the resultant peroxynitrite (Hayden et al., 2005).

STS may furthermore revert a functional vasoconstriction via the vasodilating molecule H_2S which is likely produced as a consequence of endogenous STS metabolism (Sen et al., 2008). The H_2S-induced dilatation of narrowed skin vessels could also explain the rapid reduction of the (presumably ischemic) pain, which is often seen after the start of STS therapy. The improved oxygen and nutrient supply would then - as in hyperbaric oxygen therapy – support the healing of the ulcerations.

In conclusion, the therapeutic effects of STS are probably mainly due to the neutralization of vasculature-harming reactive oxygen species and the – possibly coupled – generation of a potent vasodilator (H_2S).

The proposed mechanisms of action of STS might thus beneficially affect both, the medial calcifications and the vascular luminal narrowing. The potential of inhibition of calcium precipitation and calcium chelation is probably rather a contributing therapeutic effect of STS.

1.6 Pharmacokinetics

Thiosulfate (TS, $S_2O_3^{2-}$), the anion of STS, is an endogenous intermediate of mammalian sulfur metabolism. The endogenous synthesis of TS is accomplished by three mitochondrial enzymes, sulfur-quinone oxidoreductase (SQR), ethylmalonic encephalopathy 1 (ETHE1) and the TST enzyme (Hildebrandt and Grieshaber, 2008). The physiological excretion of TS is in the range of 10-20 µmol/day in the urine of healthy persons and depends on protein intake and likely on genetic factors (Farese et al., 2011).

Because of the free filtration of STS in the renal glomerulum, the negligible tubular handling, its low protein binding and the distribution in the extracellular space, STS was widely used as an alternative to inulin clearance measurement for the routine determination of kidney function in the 1940s to 1970s (Vorburger et al., 1969).

There are only few data on the pharmacokinetics in humans available in the literature.

In healthy volunteers, STS is poorly absorbed orally, but is rapidly distributed throughout extracellular fluid after i.v. administration. STS taken orally is not systemically absorbed. Most of the thiosulfate is oxidized to sulfate or is incorporated into endogenous sulphur compounds; a small proportion is excreted through the kidneys. Approximately 20-50% of exogenously administered STS is eliminated unchanged via the kidneys. The volume of distribution of STS is 150 mL/kg. STS is excreted in the urine, with a clearance half-life of 0.25 to 3 hours being reported when a single bolus dose of 1 g of STS is given. However, after an i.v. injection of a substantially higher dose of STS (150 mg/kg, that is, 9 g for 60 kg bw) in normal healthy men, the reported elimination half-life was 182 minutes (for details, see Investigator's Brochure).

In the absence of an intact kidney function (i.e. in dialysis patients) STS is completely metabolized endogenously and the resulting sulfate is largely removed during the next dialysis session (Farese et al., 2011). Therefore and because of a better tolerability, start of infusion of STS is recommended 30 min before the end of hemodialysis (HD) with an overall infusion duration of 60 min.

1.7 Safety profile

STS has been used in human medicine for decades. In the 1950s and 1960s it was used for the determination of renal function. An assessment of the periodic safety update reports (PSUR) since the international birthdate of STS in 1978 in Germany did not reveal critical side effects such as acute poisoning, death or any deterioration of the patient that required admission to a hospital. This assessment includes data from 24 human studies comprising more than 1,200 patients who have been treated with STS as a cancer chemoprotectant primarily for the prevention of cisplatin-induced ototoxicity.

STS seems to have an acceptable safety profile and is usually well tolerated. The most prominent side effects reported with STS are nausea and vomiting, often in patients treated with a dose of 25 g 3x per week, and are usually described as mild, temporally related to the infusion, and responsive to antiemetics and/or prokinetics. Reducing the dose or rate of infusion can be helpful. A raised anion gap metabolic acidosis is also well recognized, and can be severe (Selk and Rodby, 2011; Mao et al., 2013). This is again less of a problem with a reduced dose, but is also relatively easily managed with bicarbonate supplementation or increasing the dialysate bicarbonate.

Headache, hypotension, thrombophlebitis (when STS is given through a peripheral i.v. cannula), and hypersensitivity to smells with anorexia have been reported (Baker et al., 2007), (Musso et al., 2009), (Ong and Coulson, 2011), (Tokashiki et al., 2006).

With regard to longer-term adverse effects, there is some concern regarding the possibility of bone demineralization, with a reduction in bone strength/bone mineral density (BMD) compared with controls reported in both animal and human studies of STS. *Adirekkiat et al.* demonstrated a significant reduction in total hip BMD and a trend towards a reduction in lumbar spine BMD in 15 patients treated with 12.5 g i.v. STS twice weekly for 4-months

(Adirekkiat et al., 2010). This dose is within the dose range usually given for the treatment of calciphylaxis (6-25 g for 3x per week). The reason for the reduction in BMD is unclear, but the metabolic acidosis induced by STS treatment was proposed as a contributing factor. Another study in 22 haemodialysis patients could not detect any reduction in lumbar BMD after STS treatment for 5 months (Mathews et al., 2011). Although reports from the literature regarding bone-demineralisation effects of STS are contradictory, any bone fractures in longer-term survivors of calciphylaxis patients treated with STS should be observed and thoroughly monitored.

No other serious side effects have been reported despite the long clinical use of STS.

1.8 Animal proof-of-concept studies with sodium thiosulfate in calciphylaxis

No animal model of calciphylaxis is available. However, *Pasch et al.* used a rat model of renal failure based on addition of adenine to the diet, which produces severe interstitial nephritis and uremia, with medial vascular calcification developing within 4 weeks (Pasch et al., 2008). STS prevents calcification in this model at a dose and interval comparable to those used in humans with calciphylaxis/CUA, thus providing a scientific basis for its clinical use. This model of renal failure is associated with marked polyuria and salt wasting rather than oliguria and sodium retention in dialysis patients, which could differentially affect STS levels and calcium balance.

The authors determined whether it also prevents development of vascular calcifications in chronic kidney disease (CKD). They found inter alia that uremic rats treated by STS had no histological evidence of calcification in the aortic wall whereas almost three-fourths of untreated uremic rats showed aortic calcification. Urinary calcium excretion was elevated and the calcium content of aortic, heart and renal tissue was significantly reduced in the STS-treated compared to non-treated animals. STS treatment transiently lowered plasma ionized calcium and induced metabolic acidosis. It also lowered bone strength in the treated animals compared to their normal controls. Hence, STS prevented vascular calcifications in uremic rats, likely by enhancing acid- and/or chelation-induced urinary calcium loss (see also Investigator's Brochure).

As mentioned above, no animal model for calciphylaxis is available and therefore, the pathophysiology and histology of calciphylaxis need to be studied in human biopsies, in which calcifications can be detected. As no biopsy study has been conducted longitudinally in calciphylaxis so far, neither the putative role of media calcification nor the sequence of the occurence of the typical histologic lesions intimal proliferation, medial calcification and luminal thrombosis of the small skin vessels have been elucidated yet. Consequently, the questions whether calcification is the *primum movens* or a consequence of ischemic changes induced by intimal proliferation and luminal thrombosis awaits clarification.

2 RATIONALE

2.1 STS for the treatment of calciphylaxis

Up to now, no prospective clinical trial with STS has been performed. Reasons are that calciphylaxis is a rare condition and treatment is not focused on certain centres making feasibility studies nearly impossible. Due to the limited number of patients and the spontaneous occurrence of the disease, the recruitment of calciphylaxis patients is challenging.

The previous case reports on successful treatments of calciphylaxis patients with STS support the intention to demonstrate the efficacy and safety of STS in this patient population under the conditions of a prospectively planned clinical trial.

2.2 Rationale for the dose of STS

Studies on safety and efficacy of various STS doses and on the treatment duration of STS are not feasible in calciphylaxis due to the heterogeneity and paucity of patients.

The application of doses in the range of 12.5 to 25 g has been reported in most publications on calciphylaxis patients. This dose range is based on the experience with STS as antidote for cyanide poisoning and extravasation of chemotherapeutic agents.

Only few case reports are available on the treatment of cyanide poisoning. The dose range reported for these cases was 8-12.5 g or 0.2 g/kg bodyweight, administered as bolus injection or infusion. The treatment duration was up to 12 h.

For extravasation of chemotherapeutic agents (cisplatin), publications on more than 1200 patients are available with a dose range of 3-20 g/m^2 body surface area. Lower doses were infused over 3 to 15 min, higher doses were infused over several hours. The treatment duration was up to 12 h.

Case reports and cohort studies with more than 300 calciphylaxis patients have been published up to now (see also Investigator's Brochure). In the majority of reports, a dose of 25 g per day was used (see Investigator's Brochure, Table 14). Infusion occurred during 30-

60 min at the end or after HD. Treatment duration was up to 62 weeks. On this basis, 25 g per day 3x per week was selected as an effective starting dose. To start with lower and potentially ineffective doses is ethically not acceptable for these patients. It was observed that flares may occur after reduction to 12.5 g or less, requiring subsequent increase of the STS dose to induce improvement (Pasch, personal communication). Reduction of pain is considered a very good indicator of efficacy in calciphylaxis. Therefore, the individual dosing scheme was reported to often be adjusted based on pain response, which is usually achieved within two to three weeks after the first administration.

In the present clinical trial, the dose of 25 g will be administered i.v. as an infusion starting 30 min before end of HD over 60 min 3x per week. In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms.

In case of complete remission of the wound lesion after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4) the dose may only be reduced for safety reasons.

Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed.The change in dose is at the discretion of the investigator.

3 OBJECTIVE, STUDY DESIGN AND STUDY DURATION

The objective of this project is to study the potentially beneficial effects of STS on the course and outcome of calciphylaxis. The study population will consist of 40 patients ≥ 18 years of age with calciphylaxis. Patients will be treated with STS for at least 24 weeks. It is up to the discretion of the investigator to continue STS treatment.

The study design is a prospective, uncontrolled, multicenter, Phase 2/3 study including dialysis centers in -Europea(~~Switzerland, Germany, Austria, France~~).

The duration of the trial for each patient is expected to be up to 48 weeks plus the preceding 2 to 4 weeks run-in period.

The overall duration of the trial is expected to be approximately 4 years. The actual overall duration or recruitment may vary.

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint:

- Percent reduction of the total wound area after 24 weeks (V4) compared to baseline (V0) as assessed by 2 independent, blinded dermatologists using a serial photo documentation. The mean value of both assessments will be taken.

3.1.2 Secondary Endpoints:

- Status of skin lesions:
  - Total wound area at 8, 16, 36, 48 weeks compared to baseline (V0).
  - Complete remission of wound area.
  - Occurrence of new lesions: Time point of occurrence and – if applicable – healing as well as location of each lesion to be documented at each visit (V0 to V6).
  - Qualitative improvement of skin lesions at 8, 16, 24, 36, 48 weeks as assessed by the revised Photographic Wound Assessment Tool (revPWAT) score and evaluation of a serial photo documentation through 2 independent, blinded dermatologists.
  - Use of wound debridement

- Pain:
  - Reduction of pain in the areas of calciphylaxis after 4, 8, 16, 24, 36 and 48 weeks after start of STS treatment will be compared to baseline (V0) and assessed by a visual analogue scale (VAS) for pain (0-10). This will be done directly before changing the wound dressing.
  - Consumption of pain medication (normalized to morphine equivalent with an appropriate conversion table) will be assessed at VR, V0 and 4, 8, 16, 24, 36 and 48 weeks after start of STS treatment and compared to baseline (V0).
- Clinical global impression:
  - Change in clinical global impression as assessed by the Clinical Global Impressions-Improvement (CGI-I) score at each follow-up visit (after 4, 8, 16, 24, 36 and 48 weeks) compared to baseline (V0) and the Clinical Global Impression-Severity scale (CGI-S) through the investigators. The Clinical Global Impression-Severity scale (CGI-S) will be assessed at each visit from visit V0 to V6 (i.e. after 4, 8, 16, 24, 36 and 48 weeks).
- Improvement leading to eligibility of the patient for kidney transplantation:
  - Eligibility for kidney transplantation is given when the patient is being actively listed on a transplant waiting list.
- Bone mineral density (BMD):
  - For measurement of BMD, study sites will be evaluated for the availability of Dual Energy X-ray absorptiometry (DEXA) technique.
  - BMD will be measured at V0 and after 48 weeks (V6)
- Survival:
  - Median overall survival after start of STS treatment
  - One-year survival rate

3.1.3 Safety parameters:

- Adverse events
- AESI (incidence of infections and sepsis, metabolic acidosis, ventricular tachycardia, hypotension, bone fractures)
- Use of other concomitant medications
- Laboratory parameters (parathyroid hormone [PTH], total calcium, phosphorus, alkaline phosphatase, pH, CRP, leucocytes, hemoglobin, creatinine, albumin, Na, K, Cl, Mg, ASAT, ALAT, GGT, Amylase, Lipase, urea, uric acid, venous blood gas analysis, 1.25 vitamin D, 25 vitamin D,
- Physical examinations, ECG, vital signs (heart rate, blood pressure)

Tolerability of STS treatment

3.1.4 Biobanking

- Serum will be collected for assessing further relevant parameters, e.g. inflammatory and calcification parameters and bone turn-over markers. The evaluation of these parameters is planned to be performed within 5 years after the end of the trial.
- T50 test (in vitro blood test for calcification propensity by monitoring the maturation time (T50) of calciprotein particles in serum according to Pasch et al. (Pasch et al., 2012).

3.2 Number of patients

We aim to include a total of 40 patients in this study. Recruitment and treatment of patients is planned to be performed in dialysis centers. Further sites might be selected during the active period of the trial.

3.3 Diagnosis

At start of the run-in phase (VR) and during the run-in phase, patients will be examined by serological and histological parameters as indicated to confirm the diagnosis of calciphylaxis and to exclude other causes for necrotizing skin lesions and ulcerations.

The following differential diagnoses should be considered depending on clinical circumstances:

- peripheral arterial occlusive disease
- vasculitis
- arterial embolism
- anti-phospholipid antibody syndrome
- coumarin necrosis
- cryoglobin-related skin disorder
- heparin necrosis
- nephrogenic systemic fibrosis

The following diseases and conditions have to be excluded histologically:

- Pyoderma gangraenosum
- coumarin necrosis
- nephrogenic systemic fibrosis

If the typical clinical signs for calciphylaxis are detected, in particular more than one lesion appears, and other diagnoses can be excluded based on the results of serological and histological analyses, the diagnosis of calciphylaxis can be confirmed.

3.4 Medications and measures for best supportive care

The following measures for best supportive care (BSC) are considered obligatory:

- Cautious necrosectomy only, no debridement of wound margins!
- Keep patients dry and treat peripheral edema to support wound healing

The following measures are considered as optional and are proposed in the literature as potential treatments for calciphylaxis patients. It is at the discretion of the trial centers respectively the investigators, which measures are appropriate for treatment during the run-in phase. However, all participating centers are free in their decision how to treat their calciphylaxis patients during the run-in phase:

- Reducing ionised Ca^{2+} and PO_4^- to the lower normal range
- Stopping vitamin D compounds (25-OH, 1,25-OH, paricalcitol)
- Replacement of calcium-containing phosphate binders
- Treatment of patients having hyperparathyreoidism with high bone turnover (high alkaline phosphatase) with parathyreoidectomy or Cinacalcet
- Stopping coumarine
- Replacing coumarine with low molecular weight heparins
- Administration of vitamin K
- Avoidance of iron therapy i.v./p.o.
- Reducing skin punctures and other tissue traumata to a minimum
- If applicable, surgical therapy /plastische cover of the lesion
- Permanent administration of antibiotics
- Avoidance of phosphate-containing enemas (contraindicated in patients with renal insufficiency)
- In case of peritoneal dialysis, switch to HD
- HD eKt/V at least 1.2
- Switch to HD during daytime or long nocturnal HD
- Switch to HDF
- Dialysis against low calcium dialysate (1.25 mmol/L or lower)
- Plasmapheresis against fresh frozen plasma (FFP)
- Hyperbaric oxygen

3.5 Study treatment

At start of the run-in phase (VR) of 2 to 4 weeks, patients will be treated with conventional medications and measures as described in section 3.4. Considering the severity of the disease, the run-in period has to be limited to 2 weeks for those patients rapidly progressing under BSC while for the other patients a 4-week run-in phase is justifiable.

If the investigator observes typical symptoms of calciphylaxis (e.g. pain, appearance of more than one wound lesion) and decides that the patient is eligible for the treatment with STS and participation in the clinical trial, a biopsy will be taken to confirm the diagnosis of calciphylaxis by excluding other causes of necroses and ulcerations. If a biopsy report of a consisting wound is available at Screening (VR) and the diagnosis of calciphylaxis is confirmed or other causes for necroses and ulcerations were excluded, an additional biopsy is not required. Patients with rapidly progressive disease under BSC will be allocated to Group A while patients with less progressive or initially stable disease will be allocated to Group B. Patients in both groups will be treated with STS. Both patient groups will be analysed separately, with Group A to establish efficacy and Group B to be assessed descriptively (see section 11.2.1). Patients with severe disease status may be switched to STS treatment earlier than 2 weeks. These patients will be excluded from the Per-Protocol (PP) analysis.

Then, at V0, treatment with STS starts and will be continued for at least 24 weeks. From the long-standing experience published in the literature, a clinically meaningful reduction (>20%) in the total wound area is expected by the clinical experts after 24 weeks of STS treatment.

The dose of 25 g will be administered i.v. as an infusion starting 30 min before end of HD over 60 min 3x per week. In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms.

In case of complete remission of the wound area after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4) the dose may only be reduced for safety reasons.

Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed. The total amount of STS administered over all treatments will be calculated and recorded for each visit.

It is at the discretion of the investigator to reduce the dose to a lower dose in case of adverse effects. Treatment will continue up to 48 weeks until either complete remission, reduction in pain, reduction in wound surface, healing of ulcera, or discontinuation due to side effects occurs.

3.6 Definition of treatment response

For patients treated with BSC, wound size is typically increasing as shown in the literature and medical expert knowledge. A median reduction of the total wound area of 20% or more is clearly a clinically relevant improvement as, again based on empirical medical knowledge, wound size is correlated with the detrimental symptoms of calciphylaxis. For the current study, a median wound size reduction of 50% or more is expected.

3.7 Safety Monitoring

Safety assessments start at the time point, when the patient enters the run-in phase (VR).

If the patient is excluded from the trial at baseline (V0) because the diagnosis of calciphylaxis cannot be confirmed or because the patient withdraws the consent for STS treatment, the patient will not be followed up in the trial beyond that time point for further assessments of safety parameters.

Safety parameters will include adverse events, concomitant pain and other medications, physical examinations, ECG, vital signs, standard clinical laboratory evaluations (as described in section 3.1.2), and tolerability of STS treatment.

4 PATIENT SELECTION

4.1 Inclusion Criteria

(1) All patients ≥ 18 years

(2) Male or female HD patients with a diagnosis of calciphylaxis. (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching).

(3) Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study

4.2 Exclusion Criteria

(1) Sodium metabisulfite hypersensitivity, among others the history of bronchial asthma due to known sodium metabisulfite hypersensitivity

(2) Females who are pregnant (positive pregnancy test at screening or during study phase), lactating, or, if having reproductive potential (being not post-menopausal* or surgically sterilized) are considered potentially ineligible with respect to use highly effective** methods of birth control throughout the study, which are also described in detail in the Patient Inform Consent Form. (Of note, STS has been demonstrated not to cross the blood-placenta barrier in gravid eves (Graeme et al., 1999); therefore we regard fetal damage also as unlikely in humans).

(3) Patients who have participated in any other investigational studies within 30 days previous to enrollment

(4) History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment.

(5) Good response to conventional treatment.

(6) Life expectancy less than 4 months in the judgement of the investigator

*: Post-menopausal: no menses for 12 months without an alternative medical cause

**: Highly effective methods of birth control: methods that alone or in combination result in a failure rate less than 1% per year when used consistently and correctly. A combination of two of the following methods is considered highly effective:
a) use of oral, injected or implanted hormonal methods of contraception (in the case of oral contraception, the same pill at the same dosage for at least 3 months before taking the study medication)
b) placement of an intrauterine device (IUD) or intrauterine system (IUS)

c) use of barrier methods (diaphragm or cervical cap, which are not made of latex) in women, or the use of a condom by male partner in combination with a spermicidal foam/gel/coating/cream/vaginal suppository

4.3 Concomitant medications

All medications taken by the patients for treatment of the symptoms of calciphylaxis during the run-in phase and the subsequent STS treatment phase will be recorded in the eCRF with actual dose, duration of treatment and indication up to 48 weeks.

4.4 Patient Withdrawal

Patients are free to withdraw from the study at any time for any reason. In addition, patients may be withdrawn from the study by the Principal Investigator or Sub Investigator for the following reasons:

- Adverse events (e.g. uncontrollable infections, pain, nausea),
- progression despite treatment,
- severity of the disease

The clinical report will include reasons for patient withdrawals as well as details relevant to the patient withdrawal. If a patient is withdrawn from the trial prior to study completion, he/she will undergo all procedures scheduled for study completion

4.5 Premature Closure of the Clinical Trial

The trial can be prematurely closed or suspended by the Coordinating Investigator or the sponsor in case that new risks for patients become known. The Ethics Committee (EC) and the competent regulatory authorities must then be informed. Furthermore, the EC and competent regulatory authorities themselves may decide to stop or suspend the trial.

Should the trial be closed prematurely, all trial material (investigational medicinal products, etc.) must be returned to the Sponsor.

All involved investigators have to be informed immediately about a cessation/ suspension of the trial. The decision is binding to all trial center's and investigators.

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4.6 Treatment Assignment

The trial medication will be administered only to patients included in this trial.

Patients withdrawn from the trial retain their identification codes. New patients must always be allocated a new identification code.

4.7 Dosing of the study medication

At start of the run-in phase (VR) of 2 to 4 weeks, patients will be treated with conventional medications and measures as BSC (see section 3.4). If the investigator observes typical symptoms of calciphylaxis (e.g. pain, appearance of more than one wound lesion) and decides that the patients is eligible for the treatment with STS and participation in the clinical trial, a biopsy will be taken to confirm the diagnosis of calciphylaxis by excluding other causes of necroses and ulcerations. If a biopsy report of a consisting wound is available at Screening (VR) and the diagnosis of calciphylaxis is confirmed or other causes for necroses and ulcerations were excluded, an additional biopsy is not required. Then, patients will be treated with STS (V0).

The dose of 25 g will be administered i.v. as an infusion starting 30 min before end of HD over 60 min 3x per week. In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms.

In case of complete remission of the wound lesion after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4) the dose may only be reduced for safety reasons.

Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed in the eCRF.

It is at the discretion of the physician to reduce the dose to the next-lower dose in case of adverse effects.

Treatment will continue up to 48 weeks (V6) until either complete remission, reduction in pain, reduction in wound surface, healing of ulcera, or discontinuation due to side effects occurs.

4.8 Packaging and Labelling

The trial medication will be labelled according to GCP requirements.

4.9 Supplies and Accountability

The investigator will keep an account of the trial medication and acknowledge the receipt of all shipments of the trial medication.

The investigator will also keep accurate records of the quantities of trial medication used for each patient. The documentation has to include date of application, patient identification, batch/ serial numbers or other identification of trial medication. The site monitor will periodically check the supplies of trial medication held by the investigator to ensure the correct accountability of all trial medication used. At the end of the trial, all unused trial medication and all medication containers will be completely returned to the sponsor. It will be assured that a final report of the drug accountability is prepared and maintained by the investigator.

5 CONDUCT OF THE TRIAL AND STUDY ASSESSMENT SCHEDULE

The study shall be performed according to the following chronological steps, which are depicted hereafter and in Figure 1 and Flow Chart (Table 1).

5.1 Identification and inclusion of a calciphylaxis patient in the trial center

Patients with calciphylaxis are typically identified in dialysis centers.

A first diagnosis of suspected calciphylaxis will be performed according to the typical signs and symptoms (severe pain, livedo, violaceous plaques, ulcerations, necroses) and by excluding other causes of necroses and ulcerations as described in section 3.3.

Each patient will be identified by a 7-digit patient number, which is a combination of the 2-digit county number, the 2-digit site number and a unique 3-digit number. The country number (eg 01, 02 etc.) and site number (eg 01, 02 etc.) will be assigned by the CRO, the unique 3-digit number will be assigned to the patient by the investigator, starting with 001. For example, the patient number for the first patient in country 01 at site 01 will be 01-01-001.

At start of the 2 to 4-week run-in phase (VR), the patient will be informed about the character and individual consequences of the clinical trial and has to provide written informed consent to participate in the study.

Upon decision of eligibility of the patient to participate in this clinical trial by fulfilling all inclusion and no exclusion criteria, the diagnosis, medical history and demographic data, including sex, age, race, body weight (kg), height (cm), BMI and tobacco use will be recorded in the eCRF. Each patient will have a physical examination, vital sign measurements (heart rate, blood pressure, ECG), and the laboratory tests. Then, the patient will be treated with conventional medications and measures (see section 3.4).

If the investigator assesses the patients as eligible for the treatment with STS, a biopsy will be taken and analyzed during the run-in phase to confirm the diagnosis of calciphylaxis by excluding other causes of necroses and ulcerations. Additionally at the end of the study all biopsy samples will be analyzed centrally.

When the diagnosis of calciphylaxis has been confirmed, the patient will be asked again if he/she agrees to participate in the clinical trial and to undergo STS treatment.

The run-in phase will end on the same day, when patients will start treatment with STS (baseline, V0).

5.2 Photo documentation and assessment of the wound area

Photo documentation of all skin lesions (total wound area) will be performed at VR, V0 (baseline), V2 (8 weeks), V3 (16 weeks), V4 (24 weeks), V5 (36 weeks) and V6 (48 weeks, end of study) to follow progression as well as remission. A graded straight edge including a colored scale will be added at the edge of the wound. The photographs will be taken under common circumstances in the in-and outpatient departments without any additional light sources; flash light should be avoided if possible. On the photographs, the necrosis/ulcers and the surrounding skin will be included.

To avoid possible bias in the assessment of the wound area, it is important to choose a camera position perpendicular to the approximate center of the wound. The distance between camera and wound should be about 50 centimeters. This distance should not even be decreased for small wounds as smaller distances lead to image distortions especially if the wounds are located on curved surfaces. Instead, the zoom of the camera should be used as it does not create this type of distortions.

Nevertheless, wounds on strongly curved surfaces (arms, etc.) may not fit one photograph. In this case, several images of the same wound should be taken. To allow the later area assessment, pencil marks (for example small arrows) should be placed on the healthy skin at the border on the wound before the photographs are taken to denote, which part of the wound gets measured on image 1 and which on image 2.

For the measurement of the skin lesion, the inner edge of the wound will be taken. The area of each lesion will then be analyzed using the software package ImageJ.

An example is provided in Figure 2 demonstrating the assessment of the wound area in a calciphylaxis patient at start of STS treatment (calculated area is 68.6 cm^2).

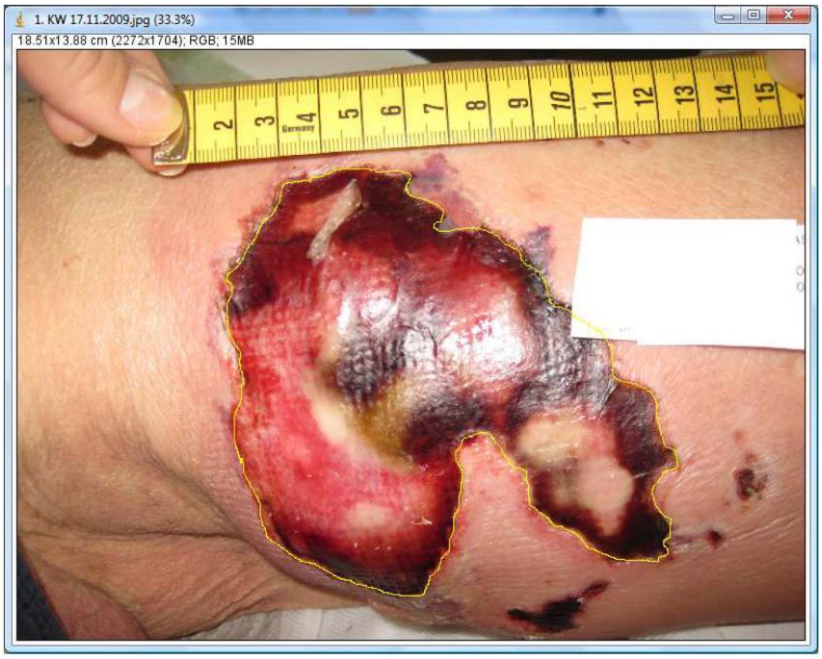

Figure 2: Photograpic documentation and assessment of wound area with the ImageJ software at start of STS administration in calciphylaxis patients

Changes in the appearance of the wounds will be assessed on the photographs by the blinded dermatologists using the revPWAT score (Thompson et al., 2013). This validated score consists of 8 domains with possible scores ranging between 0 and 32, with zero representing a completely healed wound (Figure 3). In case of missing efficacy scores (e.g. patient passes away or withdraws from the trial at later time points), the missing values will be imputed as described in 11.2.4 and the patient will be included in the efficacy analysis.

Figure 3: Photographic Wound Assessment Tool – revised (revPWAT)

Item	Assessment	Score
1. Size	0 = wound is closed (skin intact) or nearly closed (<0.3 cm^2) 1 = 0.5 – 2.0 cm^2 2 = 2.0 – 10.0 cm^2 3 = 10.0 – 20.0 cm^2 4 = > 20.0 cm^2	
2. Depth	0 = wound is healed (skin intact) or nearly closed (<0.3 cm^2) 1 = full thickness 2 = unable to judge because majority of wound base is covered by yellow/black eschar 3 = full thickness involving underlying tissue layers 4 = tendon joint capsule visible/bone present in wound base	
3. Necrotic tissue type	0 = none visible or wound is closed (skin intact) or nearly closed (<0.3 cm^2) 1 = majority of necrotic tissue is thin white/gray or yellow slough 2 = majority of necrotic tissue is thick, adherent white yellow slough or fibrin 3 = majority of necrotic tissue is white/grey devitalized tissue or eschar 4 = majority of necrotic tissue is hard grey to black eschar	
4. Total amount of necrotic tissue	0 = none visible in open wound or wound is closed (skin intact) or nearly closed (0.3 cm^2) 1 = < 25% of wound bed covered 2 = 25% to 50% of wound covered 3 = > 50% and < 75% of wound covered 4 = 75% to 100% of wound covered	
5. Granulation tissue type	0 = wound is closed (skin intact) or very close to closed (<0.3 cm^2) 1 = majority (>50%) of granulation tissue is healthy looking (even, bright red appearance) 2 = majority of granulation tissue is unhealthy (eg, pale, dull, dusky, hypergranulation) 3 = majority of granulation tissue is damaged, friable, degrading 4 = there is no granulation tissue present in the base of the open wound (all necrotic)	

Figure 3: continued

6. Total amount of granulation tissue	0 = Wound is closed (skin intact) or very close to closed (<0.3 cm^2) 1 = 75% to 100% of open wound is covered with granulation tissue 2 = >50% and <75% of open wound is covered with granulation tissue 3 = 25% to 50% of wound bed is covered with granulation tissue 4 = <25% of wound bed is covered with granulation tissue			
7. Edges (directly touching and within 0.5 cm of wound edge)	0 = Wound is closed (skin intact) or very close to closed (<0.3 cm^2) or edges are indistinct, diffuse, not clearly visible because of re-epithelialization 1 = majority of edges (>50%) are attached with an advancing border of epithelium 2 = majority of edges (>50%) are attached even with wound base (not advancing) 3 = majority of edges(>50%) are unattached and/or undermined 4 = majority of edges are rolled, thickened or fibrotic (do not include callus formation)			
8. Periulcer skin viability (consider skin visible in photo or within 10 cm of wound edge)	Number of factors affected 0 = None 1 = One only 2 = 2 or 3 3 = 4 or 5 4 = 6 or more	• callus • dermatitis • maceration • desiccation or cracking • bright red erythemic	• edema • excoriation • skin tearing/irritation related to wound dressing or tape • hypo-/hyperpigmentation • other: _____	
Total score				

5.3 Biopsy taking and histological assessment

A biopsy will be taken a few days before the end of the run-in phase to confirm the diagnosis of calciphylaxis by excluding other causes for necroses and ulcerations. If a biopsy report of a consisting wound is available at Screening (VR) and the diagnosis of calciphylaxis is confirmed or other causes for necroses and ulcerations were excluded, an additional biopsy is not required.

Spindle shapes skin biopsies will be taken in the participating centers by excision of an approximately 2 x 0.6 cm spindle-shaped piece of skin, radially involving healthy and calcified plaque-like skin, or healthy skin and the border of an ulcerative lesion.

Alternatively, a deep 5 mm punch biopsy will be taken from the border of the affected skin area. The biopsy wound can thereafter stay open or should be closed by a surgical suture, depending on heaviness of bleeding.

The biopsy will be analyzed by Alzain and Kossa stainings to detect calcification and thus, to confirm the condition of calciphylaxis or for exclusion of other causes of necrosis and/or ulceration of the skin.

5.4 Assessment of Bone Mineral Density (BMD)

The contract research organisation (CRO) performing the initiation of the study sites and monitoring for the clinical trial will evaluate the availability of DEXA scanners and the possibility to use this technique for determining the BMD in calciphylaxis patients at baseline (V0) and after 48 weeks (V6).

Dual **E**nergy **X**-ray **A**bsortiometry, or DEXA scanning, is currently the most widely used method and the most reliable technique for measurement of bone mineral density (BMD) for several reasons. DEXA is the clinical standard for measurement of BMD. DEXA scanners use an X-ray rather than gamma ray source to emit dual energy photons. The advantages of this technique are shorter scan time, lower radiation exposure (less than 3 mRem), higher precision and less expensive. DEXA scanning is more sensitive and accurate at measuring subtle changes in bone density over time or in response to drug therapy than is Qualitative computed tomography (QCT).

For the test, a patient lies down on an examining table, and the scanner rapidly directs x-ray energy from two different sources towards the bone being examined in an alternating fashion at a set frequency. BMD will be measured in the hip and spine. In certain situations – e.g. if the hip or spine cannot be measured - BMD will be measured in the forearm. The mineral density of the patient's bone weakens, or prolongs the transmission of these two sources of x-ray energy through a filter onto a counter in a degree related to the amount of bone mass present. The greater the bone mineral density, the greater the signal picked up by the photon

counter. The use of the two different x-ray energy sources rather than more traditional radioisotope studies (such that would be used for a bone scan) greatly improves the precision and accuracy of the measurements.

5.5 Administration of STS

Upon confirmation of the condition of calciphylaxis by analysis of the biopsy, STS will be administered i.v. as an infusion over 60 min 3x per week by starting 30 min before end of HD at V0 (baseline).

In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms.

In case of complete remission of the wound lesion after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4), the dose may only be reduced for safety reasons.

Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed in the eCRF.

The association of the total amount of administered study drug and the treatment effect will be plotted and analyzed using a linear regression model.

5.6 Documentation of pain on a visual analogue-pain scale

Degree of pain will be assessed at start of the run-in phase (VR), at baseline (V0), and directly before changing wound dressings at 4 (V1), 8 (V2), 16 (V3), 24 (V4), 36 (V5) and 48 weeks (V6). The patient has to indicate his/her experience of present pain in the area of the wound lesions on a visual analogue scale (VAS) (0-10, i.e. no pain (=0) to worst pain imaginable (=10)).

A 10-20% decrease in pain intensity is considered minimally important, at least 30% decrease is moderately important, and more than 50% decrease is a substantial improvement (Breivik et al., 2008).

5.7 Documentation of pain medication and other concomitant medications

All participating centers are – apart from the study medication – free in their decision how to treat their calciphylaxis patients. This means that all therapeutic measures can be applied according to BSC at the participating center. These measures including concomitant medications have to be documented in the eCRF at each dialysis visit before start of dialysis.

Consumption of pain medication will be normalized to morphine equivalent with an appropriate conversion table and will be assessed at each visit, at which the VAS will be assessed (VR, V0 and after 4, 8, 16, 24, 36 and 48 weeks).

5.8 Treatment success/change in clinical global impression

After 24 weeks (V4), appraisal of therapy success will be assessed by photo documentation of the wound status, measurement of total wound area, and assessment of pain, as indicated in Section 3.1.1 primary endpoints.

- The changes in the clinical global impression will be assessed by the Clinical Global Impression-Severity scale (CGI-S) and the Clinical Global Impressions-Improvement (CGI-I) score according to Busner and Targum (Busner and Targum, 2007). The CGI-S rates the severity of the patient's illness at the time of assessment, the CGI-I allows to quantify and track patient progress and treatment response over time. The CGI-Sscale will be assessed for the first time at baseline (V0). TheCGI-I will then be assessed at each follow-up visit (V1-V6) and will be compared to baseline CGI-S. The Clinical Global Impression-Severity scale (CGI-S) will be assessed at each visit from visit V0 to V6. The following query is rated on a seven-point scale:

"Considering your total clinical experience with this particular population, how ill is the patient at this time:

1= normal, not at all ill;

2=borderline mentally ill

3=mildly ill;

4=moderately ill;

5= markedly ill;

6=severely ill;

7=extremely ill."

"Compared to the patient's condition at the baseline visit (V0), this patient's condition is:

1=very much improved since the initiation of treatment;

2=much improved;

3=minimally improved;

4=no change from baseline (the initiation of treatment);

5=minimally worse;

6= much worse;

7=very much worse since the initiation of treatment."

5.9 Eligibility of the patients for kidney transplantation

Eligibility for kidney transplantation is given when the patient is being actively listed on a transplant waiting list.

5.10Occurrence of new lesions

The time point of occurrence and – if applicable – healing as well as the location of eachlesion will be documented in the eCRF. In order to ensure traceability of the lesions each

lesion will receive at time of occurrence a consecutive number (L1 to LX) which will be maintained throughout the study.

5.11Follow-up period up to 48 weeks

If tolerated by the patient, the dose of 25 g 3 x per week should be applied up to 24 weeks (V4) to assess the efficacy of this dose for the primary endpoint. During the continuing period up to 48 weeks, either continuation or slow reduction of STS dosing may occur as needed by the patient or in case of complete wound healing after at least 24 weeks of treatment. If cessation of STS is decided by the investigator for safety reasons (allowed at any time) or because of complete wound healing (only allowed after 24 weeks of treatment), a restart of STS treatment is possible in case of flares and recurrence of symptoms. Each change in dosing, stop of administration of STS and restart of STS treatment has to be recorded in the eCRF.

5.12Laboratory parameters

At start of the run-in phase (VR), at baseline (V0), and after 8, 16, 24 and 48 weeks, blood sampling and freezing of a 10 ml serum vial directly before dialysis has to be performed for analysis of laboratory parameters (PTH, total calcium, phosphorus, alkaline phosphatase, pH, CRP, leucocytes, hemoglobin, creatinine, albumin, Na, K, Cl, Mg, ASAT, ALAT, GGT, Amylase, Lipase, urea, uric acid, venous blood gas analysis (pH, pO_2, SB), 1.25 vitamin D, 25 vitamin D). Analysis of these blood parameters will be performed locally at the respective study site.

The T50 test will be conducted to obtain information on the calcification propensity by monitoring the maturation time (T50) of calciprotein particles in serum (Pasch et al., 2012). For this test, about 2 ml blood samples (serum) will be taken at the respective time points (VR, at baseline (V0), and after 8, 16, 24 and 48 weeks). Labelled tubes will be provided to the study site by the central laboratory. The analysis of the samples will be done within 5 years after end of study by the company Calcisco AG, Switzerland. Remaining samples will be destroyed at the Calcisco AG.

For establishing a biobank for calciphylaxis, blood samples (serum) will be analyzed for relevant parameters, e.g. inflammatory and calcification parameters and bone turn-over markers At each time point of blood sampling (see above), additionally 10 ml serum will be taken. Labelled tubes will be provided to the study site by the central laboratory..

All samples will be shipped on dry ice to the central laboratory on the day of collection and are stored centrally at -80°C until analysis will be performed.

5.13Soft tissue radiographs - optional

It is optional, i.e. at the discretion of the investigator to take soft tissue radiographs using mammography x-ray technique at baseline (V0) to assess the status of soft tissue calcifications in the areas of the skin lesions.

5.14Safety Monitoring

Several adverse events, which may occur during the course of the study, are caused by the underlying and often long-lasting disease/condition of calciphylaxis patients.

Adverse events (AEs) will therefore be entered into the eCRF, if they are evaluated as new symptom/medical condition, as AE of special interest (AESI), new diagnosis, changes of laboratory parameters, intercurrent diseases and accidents, recurrence of disease, increase of frequency or intensity of episodical diseases, according to the definition of AEs in section 7.1.1. However, all serious AEs (SAEs) need to be recorded in the eCRF. All patients will be followed for AEs and SAEs for 7 days following the last dose of STS.

Details of assessment and reporting of adverse events are presented in Section 7.

5.15Study Flow Chart

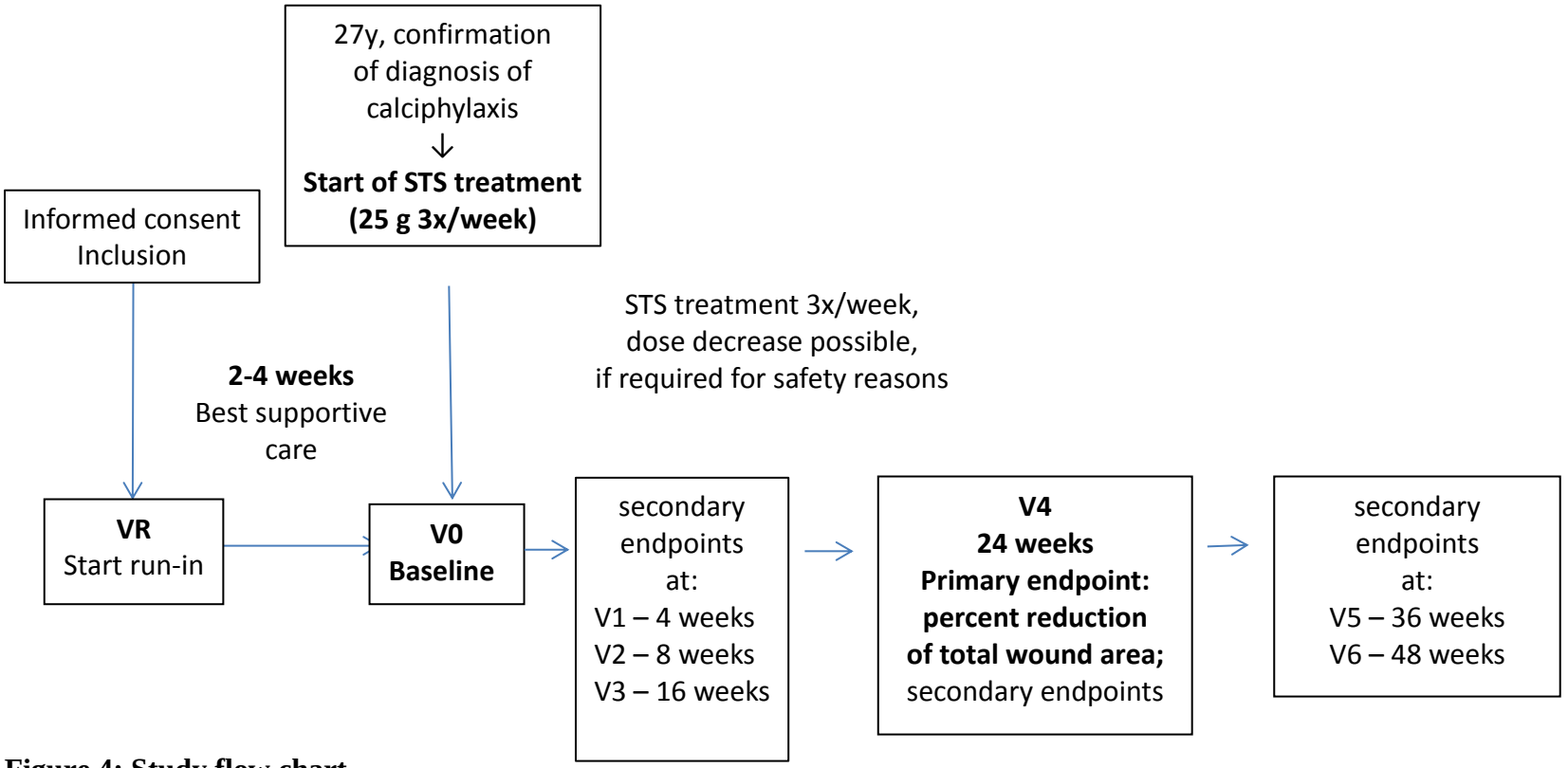

Figure 4: Study flow chart

Table 1: Flow Chart

	Screening	**VR** **Start of run-in phase;** **duration of 2 to 4 weeks**	**V0** **end of run-in = baseline**	**V1** **4 weeks**	**V2** **8 weeks**	**V3** **16 weeks**	**V4** **24 weeks**	**V5** **36 weeks**	**V6** **48 weeks**	**SFU 1** **0.5 year after treatment**	**SFU 2** **1 year after treatment**
Informed consent of the patient	X		X								
Physical examination, vital signs, ECG[1]		X	X	X	X	X	X	X	X		
Inclusion and exclusion criteria,	X		X								
Demographics, baseline characteristics		X									
Skin biopsy for diagnosis of calciphylaxis			X[2]								
Soft tissue radiographs (optional)			(X)								

	Screening	**VR** **Start of run-in phase;** **duration of 2 to 4 weeks**	**V0** **end of run-in = baseline**	**V1** **4 weeks**	**V2** **8 weeks**	**V3** **16 weeks**	**V4** **24 weeks**	**V5** **36 weeks**	**V6** **48 weeks**	**SFU 1** **0.5 year after treatment**	**SFU 2** **1 year after treatment**
Documentation of total wound area (photograph and calculation of wound size)		X	X		X	X	X	X	X		
revPWAT score		X	X		X	X	X	X	X		
Laboratory parameters (including samples for biobanking)		X	X		X	X	X		X		
VAS for pain (0-10)[3]		X	X	X	X	X	X	X	X		
Pain medication requirement		X	X	X	X	X	X	X	X		
Other concomitant medication/measures (e.g. wound debridement)		X	X	X	X	X	X	X	X		
CGI-I				X	X	X	X	X	X		
CGI-S			X	X	X	X	X	X	X		

	Screening	VR Start of run-in phase; duration of 2 to 4 weeks	V0 end of run-in = baseline	V1 4 weeks	V2 8 weeks	V3 16 weeks	V4 24 weeks	V5 36 weeks	V6 48 weeks	SFU 1 0.5 year after treatment	SFU 2 1 year after treatment
Occurrence of new lesions under STS treatment				X	X	X	X	X	X		
BMD (optional)			X						X		
Pregnancy Test		X	X	X	X	X	X	X	X		
Adverse events		X	X	X	X	X	X	X	X		
Survival rate										X	X

[1] ECG only during physical examination at start of run-in phase

[2] If patient is assessed by the investigator as eligible for STS treatment. If a biopsy report of a consisting wound is available at Screening (VR) and the diagnosis of calciphylaxis is confirmed or other causes for necroses and ulcerations were excluded, an additional biopsy is not required.

[3] VAS for pain will be assessed directly before change of wound dressing.

SFU – survival follow-up

6 PLAN FOR TREATMENT OR CARE AFTER THE TRIAL

Patients, who will need further treatment after the end of this clinical trial, will be treated according to current BSC at the respective study site.

Follow-up telephone interviews with the investigators 0.5 and 1 year after the end of the trial are planned (disease status, continuation of STS-treatment, survival, further/additional treatment and new medication for treatment of calciphylaxis).

7 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE may be:

- New symptom/ medical condition,
- New diagnosis,
- Changes of laboratory parameters,
- Intercurrent diseases and accidents,
- Recurrence of disease,
- Increase of frequency or intensity of episodical diseases.

A pre-existing disease or symptom will not be considered an adverse event unless there will be an untoward change in its intensity, frequency or quality. This change will be documented by an investigator.

All AEs (inclusive SAEs) will be documented on an electronic AE-form. AEs are classified as "non-serious" or "serious".

7.1.2 Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) are those events thought to be (potentially) associated with the investigational compound or disease under study. Despite treatment with BSC in the run-in phase or with STS in the study period, calciphylaxis lesions may progress leading to infections, sepsis and potentially to death. Cases were reported where sepsis in

calciphylaxis patients under STS treatment led to death (Norris et al., 2005), (Mataic and Bastani, 2006), (Auriemma et al., 2011). Therefore, infections and sepsis will be assessed as AESIs.

Other AESIs potentially related to STS are the occurrence of metabolic acidosis (Zitt et al., 2013), ventricular tachycardia (Amin et al., 2010), hypotension (Nigwekar et al., 2013), and bone fractures (Adirekkiat et al., 2010). More information about these adverse events is provided in the Investigator's Brochure (IB).

7.1.3 Serious Adverse Event

A serious adverse event (SAE) is one that at any dose (also overdose):

- Results in death,
- Is life-threatening (the term life-threatening refers to an event in which the patient was at risk of death at the time of event and not to an event which hypothetically might have caused death if it was more severe),
- Requires patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/ incapacity,
- Is a congenital anomaly/ birth defect.

All SAE will additionally be documented on an electronic SAE-form.

7.1.4 Expectedness

An 'unexpected' adverse event is one the nature or severity of which is not consistent with the applicable product information, e.g. Investigators Brochure. Furthermore, reports which add significant information on specificity or severity of a known adverse reaction constitute 'unexpected' events.

7.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SAEs that are both suspected, i.e. possibly related to the IMP and 'unexpected', i.e. the nature and/ or severity of which is not consistent with the applicable product information (IB or SmPC) are to be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs).

In case, either the investigator who primary reported the SAE or the second assessor classify the SAE as 'suspected', i.e. related to the IMP and the SAE is 'unexpected' it will be categorized as a SUSAR.

All SUSARs are subject to an expedited reporting to the responsible EC, the competent regulatory authority and to all participating investigators.

7.2 Period of Observation and Documentation

AEs will be documented from a time of the study inclusion up to end of the study up to 48 weeks. All patients who present AEs, whether considered associated with the use of the trial medication or not, will be monitored by the responsible investigator to determine their outcome. The clinical course of the AE will be followed up until resolution/normalization of changed (laboratory) parameter or until it has changed to a stable condition.

Each AE has to be classified in respect to the following five characteristics:

7.2.1 Intensity of the AE

The classification of intensity in this trial will be carried out on the basis of a 3-grade scale as follows:

Mild: signs and symptoms which can be easily tolerated. Symptoms can be ignored or disappear when the patient is distracted.

Moderate: symptoms cause discomfort but are tolerable, they cannot be ignored and affect normal activity.

Severe: symptoms strongly affect normal activity.

7.2.2 Relatedness of the AE to the IMP

The investigator will evaluate each AE that occurred after patient's study inclusion regarding the coherency with the administration of the investigational medicinal product. There will be following criteria for classification in respect to the relatedness to the IMP:

'related': There is a reasonable possibility that the event may have been caused by IMP. A certain event has a **strong temporal relationship** and an

alternative cause is unlikely.

‘probable’: An AE that has a reasonable possibility that the event is likely to have been caused by IMP. The AE has a **timely relationship** and **follows a known pattern of response**, but a potential alternative cause may be present.

‘possible’: An AE that has a reasonable possibility that the event may have been caused by IMP. The AE has a **timely relationship** to the IMP; **however, the pattern of response is untypical**, and an alternative cause seems more likely, or there is significant uncertainty about the cause of the event.

‘unlikely’: Only a remote connection exists between the IMP and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event.

‘not related’: An AE that does not follow a reasonable temporal sequence related to the IMP and is likely to have been produced by the patient’s clinical state, other modes of therapy or other known etiology.

‘not assessable’: The relationship between an AE and the IMP that does not follow a reasonable temporal sequence from trial participation and that is likely to have been produced by the patient’s clinical state, other modes of therapy or other known etiology.

7.2.3 Outcome of the AE

The outcome of an AE at the time of the last observation will be classified as:

‘Recovered/ resolved’:

all signs and symptoms of an AE disappeared without any sequel at the time of the last interrogation,

'Recovering/ resolving':
the intensity of signs and symptoms has been diminishing and/ or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution,

'Not recovered/ not resolved':
signs and symptoms of an AE are mostly unchanged at the time of the last interrogation,

'Recovered/ resolved with sequelae:
actual signs and symptoms of an AE disappeared but there are sequelae related to the AE,

'Fatal': resulting in death. If there are more than one adverse event only the adverse event leading to death (possibly related) will be characterized as 'fatal',

'Unknown': the outcome is unknown or implausible and the information cannot be supplemented or verified.

7.2.4 Action taken with the IMP

The action taken with IMP will be assigned to one of the following categories:

'Dose not changed': no change in the dose of IMP,

'Dose reduced': reduction in the dose of IMP,

'Dose increased': increase in the dose of IMP,

'Drug withdrawn': discontinuation of IMP,

'Unknown': the information is unknown or implausible and it cannot be supplemented or verified,

'Not applicable': the question is implausible (e.g. the patient is dead).

7.2.5 Countermeasures

The term 'Countermeasures' refers to the specific actions taken to treat or alleviate adverse events or to avoid their sequelae. Following categories will be used to categorize the countermeasures to adverse events:

'None': no action taken,

'Drug treatment': newly-prescribed medication or change in dose of a medication,

'Others': other countermeasures, e.g. an operative procedure.

7.3 Reporting of Serious Adverse Events by Investigator

All SAEs (including SAEs resulting in death) must be reported by the investigator to the responsible medical monitor of the CRO within 24 hours after the SAE becomes known using the "Serious Adverse Event" form.

Any SAE should be reported to

Name	Assign Safety Desk
Fax	+43 (0) 512 281514 77
Phone	+43 (0) 676 844033835
E-mail	safetydesk@assigndmb.com

The initial report must be as complete as possible including details of the current illness and (serious) adverse event and an assessment of the causal relationship between the event and the trial medication.

In addition, expedited and periodic reporting to regulatory Authorities and IRBs/ECs will be performed in accordance with local requirements. Further reporting details can be found in the study-specific SAE procedure Manual which is in accordance with respective EU requirements, International Conference on harmonization (ICH) GCP, national laws and site-specific requirements.

7.4 Expedited Reporting

SUSARs are to be reported to the EC, competent higher federal authority and to all participating investigators within regulative defined timelines, i.e. they are subject to an expedited reporting.

Investigators participating in this trial will report all SUSARS to Assign Safety Desk as soon as possible but not later than 24 hours after their notification. The reporting will be performed by faxing of a completed 'SAE Form'.

A second assessment and expedited reporting to EC and regulatory authorities will be performed by the sponsor and Assign Safety Desk; details and responsibilities of these pharmacovigilance activities will be defined in a Safety Management plan.

7.5 Emergency Unblinding

not applicable.

7.6 Emergency Treatment

During and following a patient's participation in the trial, the investigator will ensure that adequate medical care is provided to a patient for any AE, if required. The investigator will inform a patient when medical care is needed for intercurrent illness of which the investigator became aware.

8 DATA MANAGEMENT

8.1 Data collection and handling

All protocol-required information collected during the trial must be entered by the investigator, or a designated representative, in the eCRF. Patient data will be coded (see also section 10.3). The investigator, or a designated representative, should complete the eCRF pages as soon as possible after the information is collected, preferably on the same day when a patient is seen for an examination, treatment, or any other trial procedure. Any pending entries must be completed immediately after the final examination. Explanation should be given for all missing data.

The CRO will check completeness, validity and plausibility of data by validating programs, which will generate queries. The investigator or the designated representative is obliged to clarify or explain the queries. The data management is accomplished with the appropriate SOPs valid.

8.2 Electronic Case Report Forms (eCRF)

The case report form represents a faithful reflection of the trial plan requirements.

All data required by the protocol will be carefully and uninterruptedly recorded in the eCRF. eCRF entries and corrections will only be performed by study site staff authorized by the investigator. Each user is informed by the CRO of the clinical study web-site internet address and is allocated to a user account with a personal password to access the confidential web site. The personal password must be kept confidentially and must only be used by the person to whom it was assigned. For additional authorized users at the site, a new user account needs to be requested to ensure that each entry/change can be allocated to the person who performed the entry/change. All visit data need to be recorded in the database as soon as possible after each visit.

Corrections may be requested as follows:

- Investigators' responses are checked as they are entered and are rejected if they do not fulfill quality criteria. A message will specify the type of error and assist in its correction.

- If required, the CRA can ask for information to be corrected during monitoring.
- Computerized data-check programs and manual checks will identify clinical data discrepancies for resolution. Corresponding queries will be created within the system and the site will be informed about new issues to be resolved on-line.

All discrepancies will be solved on-line directly by the investigator or by authorized staff.

8.3 Storage and archiving of data

All important trial documents will be archived by the sponsor for at least 10 years after the trial termination.

The investigator(s) will archive all trial data (source data and Investigator Site File (ISF) including patient identification list and relevant correspondence) according to the section 4.9 of the ICH Consolidated Guideline on GCP (E6) and to local law or regulations.

If a patient withdraws the consent to participate in this study or if the participation will be finished prematurely by the sponsor or the Investigator, the data and samples recorded up to that point will be eligible for study related analysis. All recorded data up to that point will be anonymised after analysis. The Patient will be informed about this procedure in the Inform Consent Form.

9 STUDY MONITORING

9.1 Monitoring

The study will be performed in accordance with Good Clinical Practice and will thus require regular monitoring visits. Monitoring will be done by personal visits from a clinical monitor. Monitoring visits will occur based on patient accruals and availability of entries into the eCRFs. The monitor will review the entries into the eCRFs on the basis of source documents. Details of monitoring (i.e. frequency of visits and/or extent of Source Data Verification (SDV)) will be specified in the monitoring manual for this trial. Between these visits, contacts with study site personnel will be made by telephone, by fax or by mail, to ensure that the trial is conducted according to the protocol and the regulatory requirements.

Prior to the monitor's visit, the investigator will make sure that all data are recorded in the eCRFs. The investigator will allow the monitor access to the "source" data and essential documents and must provide support at all times to the monitor.

During the monitoring visit, the monitor will check with the investigator the progress of the trial and protocol compliance as assessed by the data recorded in the eCRFs. The investigator(s) must agree to permit the monitor to be present to observe the study procedure in one or more patients.

9.2 Source Documents

For each patient included in the study, a specific file (i.e., institution file) must exist with original data, on which is based the information recorded in the eCRF.

Source documents and eCRFs must not be exact copies of each other. As a general rule, medical information that is not specifically required by the study (e.g. patient's sex, prior medical history, prior medication, etc.) must be found in source medical documents (and in the eCRF). Information specifically required by the protocol and not required by routine clinical care may be recorded directly in the eCRF without appearing in source documents. In addition, source documents must mention that the patient has been included in an investigational study. Finally, there must be no data that are inconsistent between eCRF and source documents.

9.3 Inspection / Audits

Regulatory authorities or an auditor authorized by the sponsor may request access to all source documents, eCRF, and other trial documentation. Direct access to these documents must be guaranteed by the investigator who must provide support at all times for these activities. Patients will be generally informed about this opportunity during informed consent procedure.

For Switzerland only: The Ethic committee also may request access to all source documents and trial documentations. The Access to these data must be guaranteed by the investigator.

10 ETHICAL AND LEGAL ASPECTS

10.1Good clinical practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by Good Clinical Practice (GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

10.2 Patient information and informed consent

Before being admitted to the clinical trial, the patient must consent to participate after the nature, scope, and possible consequences of the clinical trial have been explained in a form understandable to him or her. The patient must give consent in writing. The signed Informed Consent Form will be filed by the investigator.

A copy of the signed informed consent document must be given to the patient. The documents must be in a language understandable to the patient and must specify who informed the patient.

The patients will be informed as soon as possible if new information may influence his/her decision to participate in the trial. The communication of this information should be documented.

10.3 Confidentiality

The data obtained in the course of the trial will be treated pursuant to the Federal Data Protection Law.

During the clinical trial, patients will be identified solely by an individual identification code (country number, site number, patient number). The patient date of birth will not used for the identification. Trial findings stored on a computer will be stored in accordance with local data protection law and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation will be fulfilled in its entirety.

The patient consents in writing to release the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by the EC, the competent regulatory authorities and authorized persons (inspectors, monitors, auditors). Authorized persons (clinical monitors, auditors, and inspectors) may inspect the patient-related data collected during the trial ensuring the data protection law.

The investigator will maintain a patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

Patients who did not consent to circulate their coded data will not be included into the trial.

10.4 Responsibilities of investigator

The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the trial treatments, and their trial-related duties and functions.

The investigator should maintain a list of Sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

10.5 Approval of trial protocol and amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent EC as well as to the competent regulatory authority. A written favorable vote of the EC and an (implicit) approval by the

competent regulatory authority are a prerequisite for initiation of this clinical trial. The statement of EC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member. This documentation must also include a list of members of the EC present on the applicable EC meeting and a GCP compliance statement.

Before the first patient is enrolled in the trial, all ethical and legal requirements must be met. All planned substantial changes will be submitted to EC and the regulatory authority in writing as protocol amendments. They have to be approved by the EC and the regulatory authority.

The investigator and the CRO will keep a record of all communication with the EC and the regulatory authorities.

10.6 Continuous information to independent ethics committee

Persuant to GCP Ordinance, the EC and the regulatory authority will be informed of all suspected serious unexpected adverse reactions (SUSARs), SAEs resulting in death and all AEs resulting in death or being live-threatening occurring during the trial. Both institutions will be informed in case the risk/ benefit assessment did change or any others new and significant hazards for patients' safety or welfare did occur. Furthermore, a report on all observed serious adverse events (SAEs) will be submitted once a year – Developmental Safety Update Report (DSUR).

The EC and the regulatory authorities must be informed of the end of the trial. They will be provided with a summary of trial results within one year after the end of clinical phase (LPO).

10.7 Notification to regulatory authorities

The local regulatory authorities responsible for each particular investigator will be informed before the beginning, during and at the end of the trial according to the applicable regulations. Each investigator is obliged to notify his/ her local regulatory authority. This responsibility has been delegated to the CRO.

10.8 Registration of the trial

Prior to the beginning of the clinical phase (FPI), the CRO will register the trial at Current Controlled Trials (https://www.clinicaltrialsregister.eu/index.html, http://www.controlled-trials.com or http://www.clinicaltrials.gov). Thus the trial will be given a unique ISRCTN, which is a prerequisite for a publication in a peer-reviewed medical journal.

10.9 Insurance

For patients enrolled in this clinical trial, the sponsor will contract a patient insurance.

The name, address and the insurance policy number will be given to both the investigator and to each study subject prior to enrollment. Moreover a copy of the insurance conditions will be filed on site. The Patient will be informed in the Inform Consent Form about the procedures in case of any potential violations and will be instructed to contact the Principle Investigator or the Insurance Company directly. The contact details from the insurance company are also provided in the Patient Inform Consent Form.

Any impairment of health which might occur in consequence of trial participation must be notified to the insurance company. The patient is responsible for notification. The insured person will agree with all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.

During the conduct of the trial, the patient must not undergo other clinical treatment except for cases of emergency. The patient is bound to inform the investigator immediately about any adverse events and additionally drugs taken. The terms and conditions of the insurance should be delivered to the patient.

The insurance company has to be informed about all amendments that could affect the patient’s safety.

11 STATISTICAL METHODS

11.1 Methods of Statistical Analysis

Statistical methods will be described in detail in the Statistical Analysis Plan (SAP).

The trial objectives will be evaluated by statistical hypothesis testing, summary tables and figures and by data listings.

All analyses will be performed using SAS® Version 9.2 or later and SAS JMP Version

10 or later.

11.2 Analysis Sets

11.2.1 Progressors and Non-Progressors

There will be two patient groups, both receiving the same treatment medication, which will be analysed separately. Depending on whether the disease is rapidly progressing during the run-in phase, patients are either assigned to the progressor (Group A) or the non-progressor group (Group B) at the time of enrolment. The main efficacy analysis will solely be based on the progressor group while the safety analysis will be based on the pooled data from progressors and non-progressors. Additional analyses will be performed on progressors and non-progressors individually and on the pooled set. These analyses are considered as supportive.

Safety Set The safety set consists of all enrolled patients for whom infusion of study medication had been started. All safety analyses will be performed on the safety set.

11.2.2 Full Analysis Sets (FAS)

The FAS sets for progressors (Group A) and non-progressors (Group B) consist of all patients in the corresponding group for whom infusion of study medication had been started, and for whom at least one post baseline measurement of the total wound area will be available. Even though it is expected, that there will be a significant number of drop-outs, most of these drop-outs will likely occur at a later stage of the treatment, i.e. after V1 (see 11.2.4). The FAS datasets as defined here should therefore include almost all enrolled patients.

All efficacy analyses will be performed primarily on the FAS subset of the progressors group, i.e. Group A.

11.2.3 Per Protocol Set (PPS)

The PPS sets consist of all randomized patients in the corresponding group included in the FAS, but will exclude the following:

- patients violating major inclusion/exclusion criteria related to efficacy;
- patients deviating from the protocol in an extent that causes bias for efficacy evaluation (e.g. no 24-week efficacy data available);
- patients with severe disease status which may be switched to STS treatment earlier than 2 weeks.

The final exclusion of patients from the PPS will be done at the blind review meeting on an individual patient basis.

All relevant efficacy analyses will also be conducted on the PPS. These analyses are considered as supportive for the analyses performed on FAS.

11.2.4 Missing value treatment

There is a variety of possible reasons for missing values, mostly due to the very aggressive nature of the disease, the generally very bad health state of the patients and their low life expectancy. Drop-outs due to severe treatment side effects are by contrast rather unlikely, partly because STS is generally well tolerated, partly because dose reduction is a possible alternative to a complete stop of treatment.

Nevertheless, the possibly incomplete list of drop-out reasons includes nausea, extreme pain, infections, the complete stop of treatment, transplantation, or patient's death. Apart from nausea, all other reasons are likely not treatment related. It is also expected, that drop-outs will occur with an approximately constant rate. Therefore, at least V1 data should be available for most patients.

Due to the longitudinal assessment schedule of the efficacy parameters, the use of a pattern mixture model for missing value treatment will likely provide better results than the use of the Last Observation Carried Forward (LOCF) method or other simple approaches. Details will be given in the SAP.

11.3 Baseline

Baseline measurements of the relevant efficacy and safety variables will be taken after enrolment of the patient for starting of STS treatment. Change from baseline will be calculated as the difference in post-baseline versus baseline values. Selected pre-baseline measurements (from start of the run-in phase) will be analyzed exploratively.

11.4 Descriptive Statistics

Categorical data will be summarized by means of absolute and relative frequencies (counts and percentages). Continuous data will be summarized by means of the following summary statistics: number of observations, arithmetic mean, standard deviation, minimum, median, maximum and quartiles.

Where appropriate, data will be visualized by means of box-whisker plots, arithmetic mean courses over time or Kaplan-Meier Plots for censored data.

11.5 Analysis of Efficacy

The main statistical analysis of the primary efficacy variable will be performed on the FAS of the progressors group (Group A) using the missing value handling approach as described in 11.2.4 Additional analyses on the PPS will be considered as supportive. If no efficacy data has been recorded before death and cause of death will be clearly unrelated to the treatment, the patient will be removed from the analysis.

11.5.1 Primary Efficacy Analysis

Change in total wound area until between baseline and V4 (24 weeks after start of medication) will be analyzed as the primary efficacy variable. At V0 and V4 photographs of all wounds are taken according to the description in section 5.2. The size in square centimeters of each individual wound will be assessed by two independent and blinded dermatologists using appropriate image analysis software and the means of both assessments will be calculated for each time point. The dermatologists will neither know at what time point images were taken nor will they know that two sets of images show the same patient at a different time point.

The mean area of each wound of a given patient at a given time point will then be summed up over all wounds and used to calculate the percent change in wound size.

As stated before, calciphylaxis is a highly progressive disease with rapidly deteriorating skin lesions. Without treatment or treated with standard medication, a clear worsening of lesions between V0 and V4 would take place. On the other hand, based on literature data and information from physicians, a decrease in wound size of 20% or more under STS treatment can clearly be considered as clinically relevant, because wound size is correlated with the detrimental symptoms of calciphylaxis and such a decrease in wound size would be a notable improvement for patient condition.

The change in total wound area will be analyzed using a One-sample Wilcoxon Signed Rank test. The sample median together with the corresponding confidence interval will also be given.

11.5.2 Secondary Efficacy Analysis

Pain reduction and the consumption of pain medication after 4, 8, 16, 24, 36 and 48 weeks compared to baseline will both be treated as continuous variables and independently analyzed using One-sample Wilcoxon Signed Rank Tests with a pattern mixture model approach for missing data.

Untreated pain level and/or the consumption of pain medication will significantly increase over time as the disease progresses. Any significant decrease in either parameter is a strong signal for a positive treatment effect. Even though there is supposedly a strong negative correlation between the two parameters, they will be analyzed individually at an alpha level of 0.025 one sided. Additionally, for every patient, pain level and medication consumption will be plotted as a time course covering all visits from VR to V6.

Bone mineral density (BMD) will be tabulated and analyzed descriptively.

Patient survival will be tabulated descriptively and visualized using a Kaplan Meier plot. Additionally, the overall survival after start of STS treatment and the one-year survival rate will be explicitely stated.

The assessment of total wound area, skin lesions using the revPWAT score and the clinical global impression using the CGI-S scale and CGI-I score will be tabulated descriptively and plotted as a time-course using box-whisker plots.

Patients with total remission of the wound area will be listed with the corresponding time after beginning of STS treatment. The fraction of patients with total wound remission, and for these patients, descriptive statistics about time to remission will also be provided.

Accordingly, the use of wound debridement and change in the eligibility of patients for kidney transplantation will also be analyzed

11.6 Analysis of Safety

Safety and tolerability will be assessed in terms of AEs and vital signs, and laboratory parameters will be determined using the safety analysis set. The number of AEs, which are reported in addition to the symptom complexes considered as AEs from the underlying disease, and the number and percentage of patients reporting at least one AE will be summarized by system organ class (SOC), preferred term (PT), treatment group and overall. When counting patients, an AE reported more than once will be counted only once but with its highest degree of severity. An AE will be considered treatment-emergent (TEAE), if it occurs for the first time, or worsens in terms of seriousness or severity. Summaries of treatment-emergent serious AEs, AEs leading to withdrawal, AESIs and AEs by severity and relationship to study medication will be presented.

No statistical hypothesis testing is intended on safety and tolerability data.

11.7 Laboratory Parameters

All laboratory data will be analyzed using descriptive statistics. Additionally, the number of patients with laboratory values below, within and above normal range will be determined for each parameter and time point.

11.8 Sample Size Estimation

11.8.1 Calculation procedure

There is no straightforward sample size calculation possible for this study. Firstly, neither reliable estimates for the effect size nor for the variability of the treatment effect are known, secondly, a relatively high drop-out rate is expected based on data from the literature. Sample size is therefore chosen both based on rough estimates of effect size and variability and on feasibility considerations, the latter mainly effected by the low incidence of calciphylaxis. Another issue which needs to be considered is the fact that only patients with progressing calciphylaxis will be assigned to the efficacy analysis group (Group A). However it is expected, that the number of non-progressors will be very small.

Sample size calculation for the confirmatory efficacy parameter is performed using version 3.17 of the G*Power application. Power is set to 80%, maximum alpha error to 0.05 two sided corresponding to 0.025 one-sided.

11.8.2 Reduction in total wound area

Percent reduction in total wound area will be analyzed as the primary efficacy variable. A median reduction of at least 50%, significantly higher than the 20% reduction which are already considered as clinically relevant are expected for this parameter. The standard deviation for this parameter should be no higher than approximately 100%: This results in a standardized effect size (Cohen's d) of about 0.6 and a sample size of about 25 patients. This number needs to be increased for two reasons. Firstly, only patients which show progressing disease status during the run-in phase will be included in the efficacy analysis group and secondly, there is a relatively high risk of drop-outs. In a calciphylaxis study (clinicaltrials.gov identifier: NCT00568399), only 60% of the study participants actually completed the study. For the current study, patients will be analyzed if at least one post recruitment score will be available. This should be the case for the majority of the patients. Nevertheless to account for the reasons mentioned above, the sample size will be increased by 50% and a total sample size of 40 patients will be used.

This number should provide good estimates with small enough confidence intervals for both the primary and possibly also for one or more of the secondary efficacy parameters.

12 AGREEMENTS

12.1 Financing of the Clincial Trial

The clinical trial will be financed by Dr. F. Köhler Chemie GmbH.

12.2 Financial Disclosure

Before the start of the trial, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the sponsors, in the investigational product or any commercial organisation being involved in the clinical trial. The investigator has also to confirm that he/she has not entered into any financial arrangement, whereby the value of compensation paid could affect the outcome of the clinical trial.

The investigator agrees to update this information in case of significant changes.

12.3 Reports

The *CRO* will prepare the integrated report according to ICH E3, in agreement with the sponsor.

12.4 Publication

The results will be published, preferably in a Nephrological or General Medicine Journal. All information concerning the trial is confidential before publication. Paying due regard to statutory rights and duties of a university, the investigators shall be entitled to publish, in consultation with the sponsor and after completion of the research work, the scientific findings for scientific purpose. A manuscript of the intended publication must be submitted to the sponsor (Dr. F. Köhler Chemie GmbH) for scrutiny at the latest 60 days prior to publication. Proposals for changes and modifications submitted by the sponsor ought to be taken into consideration, unless said proposals interfere with the scientific nature or the neutrality of the publication. A publication of the results in an international peer-reviewed journal is planned at the end of study.

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EudraCT-Nr. 2014-002128-28

Declaration of Consent

The clinical trial STS-CSM-1/13 will be conducted in accordance with the EU recommendations on "Good Clinical Practice (GCP)". It is certified that the trial plan, the documentation file and the appendices all contain the items of information and decisions necessary for the conduct of the study, and the study will be carried out and documented in accordance with this trial plan and that the legislative provisions and the agreements described will be adhered to.

Signature list:

Name	Function	Date	Signature
Dr. Roman Petrov Dr. F. Köhler Chemie GmbH	Sponsor	14.02.2017	
Dr. Anton Klingler Assign Data Management and Biostatistics GmbH	Biostatistician		

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Dr. Anton Klingler Assign Data Management and Biostatistics GmbH	Biostatistician	10-Feb-2017	

A Prospective Multicenter Phase 2/3 Clinical Trial with Sodium Thiosulfate for the Treatment of Calciphylaxis

PROTOCOL Nr. STS-CSM-1/13

Version 3.0, 23.06.2015

EudraCT-Nr. 2014-002128-28

Sponsor:

Dr. F. Köhler Chemie GmbH

Dr. Gernot Köhler
Werner-von-Siemens-Str. 22 - 28
D-64625 Bensheim
Germany
Phone: +49-6251-1083-0
Fax: +49-6251-1083-146

Statistician:

Dr. Gerhard Vogt
PharmaLex GmbH
Harrlachweg 6
68163 Mannheim
Germany
Phone: +49-621-181538-0
Fax: +49-621-18153820

Monitoring:

Assign Clinical Research GmbH
Hainburger Strasse 33
1030 Vienna
Austria
Phone: +43 1 40 33 805 13
Fax: +43 1 403 38 05 66

SYNOPSIS

Title	**A prospective multicenter Phase 2/3 study with sodium thiosulfate for the treatment of calciphylaxis**
Study Rationale	Up to now, no prospective clinical trial with STS has been performed. Reasons are that calciphylaxis is a rare condition and treatment is not focused on certain centres. The previous case reports on successful treatments of calciphylaxis patients with STS support the intention to demonstrate the efficacy and safety of STS in this patient population under the conditions of a prospectively planned clinical trial.
Clinical Phase	2/3
Indication	Treatment of calciphylaxis
Objectives	- The objective of this project is to study the potentially beneficial effects of sodium thiosulfate (STS) on the course and outcome of calciphylaxis. - A run-in phase of 2 to 4 weeks will be established, during which patients will be treated with conventional medications and measures. If the investigator observes typical symptoms of calciphylaxis (pain, appearance of more than one wound lesion) and decides that the patient is eligible for the treatment with STS and participation in the clinical trial, a biopsy will be taken to confirm the diagnosis of calciphylaxis by excluding other causes of skin necroses and ulcerations. - Patients with rapidly progressive disease under BSC will be allocated to Group A while patients with less progressive or initially stable disease will be allocated to Group B. Patients of both groups will be treated with STS. Both patients groups will be analysed separately, with the former to establish efficacy and the latter to be assessed descriptively. It is expected, that by far the majority of patients will be in the progressor group. - The run-in phase will end on the same day, when patients will start treatment with STS (baseline, V0). - Follow-up visits will be performed after 4 (V1) 8 (V2), 16 (V3), 24 (V4), 36 (V5) and 48 weeks (V6) after start of STS treatment. **Primary Endpoint:** Percent reduction of the total wound area after 24 weeks (V4) compared to baseline (V0) as assessed by 2 independent, blinded dermatologists using a serial photo documentation. The mean value of both assessments will be taken. **Secondary Endpoints**:

	Status of skin lesions: - Total wound area at 8, 16, 36, 48 weeks compared to baseline (V0). - Complete remission of wound area. - Qualitative improvement of skin lesions at 8, 16, 24, 36, 48 weeks as assessed by the revised Photographic Wound Assessment Tool (revPWAT) score and evaluation of a serial photo documentation through 2 independent, blinded dermatologists. - Use of wound debridement Pain: - Reduction of pain in the areas of calciphylaxis after 4, 8, 16, 24, 36 and 48 weeks after start of STS treatment will be compared to baseline (V0) and assessed by a visual analogue scale (VAS) for pain (0-10). This will be done directly before changing the wound dressing. - Consumption of pain medication (normalized to morphine equivalent with an appropriate conversion table) will be assessed at VR, V0 and 4, 8, 16, 24, 36 and 48 weeks after start of STS treatment and compared to baseline (V0). Clinical global impression: - Change in clinical global impression as assessed by the Clinical Global Impressions-Improvement (CGI-I) score at each follow-up visit (after 4, 8, 16, 24, 36 and 48 weeks) compared to baseline (V0) and the Clinical Global Impression-Severity scale (CGI-S) through the investigators. The Clinical Global Impression-Severity scale (CGI-S) will be assessed at each visit from visit V0 to V6 (i.e. after 4, 8, 16, 24, 36 and 48 weeks). Improvement leading to eligibility of the patient for kidney transplantation - Eligibility for kidney transplantation is given when the patient is being actively listed on a transplant waiting list. Occurrence of new lesions: - Time point of occurrence and – if applicable – healing as well as location of each lesion to be documented at each visit (V0 to V6) Bone mineral density (BMD) - Bone scans by Dual Energy X-ray absorptiometry (DEXA) technique at baseline and after 48 weeks (V6) Survival:

	- Median overall survival after start of STS treatment - One-year survival rate **Safety parameters:** - Adverse events - Adverse events of special interest (AESI; incidence of infections and sepsis, metabolic acidosis, ventricular tachycardia, hypotension, bone fractures). - Use of other concomitant medications - Physical examinations, ECGs, vital signs (heart rate, blood pressure) - Tolerability of STS treatment - Laboratory parameters (PTH, total calcium, phosphorus, alkaline phosphatase, pH, CRP, , leucocytes, hemoglobin, creatinine, albumin), T50 test (in vitro blood test for calcification propensity by monitoring the maturation time (T50) of calciprotein particles in serum - Biobanking: collection of serum for assessing further relevant parameters, e.g. inflammatory and calcification parameters and bone turn-over markers
Study design	The study design is a prospective, open, uncontrolled multicenter, Phase 2/3 clinical trial including at least 8 dialysis centers in 3 European countries (Germany, Switzerland, Austria). Each patient will serve as his/her own control. A median reduction of at least 50% in total wound area at V4 compared to V0 is expected for patients treated with STS. This is far above the 20% wound reduction which is already considered as clinically relevant. Patients with suspected calciphylaxis will be asked if they agree to participate in the clinical trial and to undergo STS treatment, after conventional medications and measures given during the run-in phase of 2 to 4 weeks were assessed by the investigator as insufficiently or not at all effective. The study duration for each patient will be up to 48 weeks after start of STS treatment. Patients, who will need further treatment after the end of this clinical trial, will be treated according to current BSC at the respective study site. At 0.5 and 1 year after the end of the clinical trial, the investigators will be contacted again and asked about the disease status, continuation of STS treatment and survival of the patients,

	further/additional treatment and new medication for treatment of calciphylaxis.
Number of Subjects	The study population will consist of 40 dialysis patients diagnosed with calciphylaxis.
Duration of Study	The duration of participation for each patient will be up to 48 weeks plus 2 to 4 weeks run-in phase. The overall duration of the trial is expected to be approximately 4 years.
Inclusion Criteria	(1) All patients ≥ 18 years (2) Male or female hemodialysis (HD) patients with a diagnosis of calciphylaxis. (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching). (3) Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study
Exclusion Criteria	(1) Sodium metabisulfite hypersensitivity, among others the history of bronchial asthma due to known sodium metabisulfite hypersensitivity (2) Pregnant or lactating patients. As pregnancy is an extremely rare event in HD patients, a pregnancy test will only be performed in ambiguous cases. (3) Patients who have participated in any other investigational studies within 30 days previous to enrollment (4) History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment. (5) Good response to conventional treatment. (6) Life expectancy less than 4 months in the judgment of the investigator
Treatments	At start of the run-in phase (VR) of 2 to 4 weeks, patients will be treated with conventional medications and measures. If the investigators assess the patients as eligible for the treatment with STS and for participating in the clinical trial, a biopsy will be taken during the run-in phase to confirm the diagnosis of calciphylaxis by excluding other causes of necroses and ulcerations. At the end of the run-in phase, i.e. the day defined as baseline (V0), patients will be treated with STS for at least 24 weeks. The starting dose will be 25 g per day given 3x per week 30 min before end of HD over an infusion period of 60 min. In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g.

	As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms. In case of complete remission of the wound lesion after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4) the dose may only be reduced for safety reasons. Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed.
Safety Parameters	Safety assessments start at the time point, when the patient enters the run-in phase (VR). If the patient is excluded from the trial at baseline (V0) because the diagnosis of calciphylaxis cannot be confirmed, other eligibility criteria are not met or because the patient withdraws the consent for STS treatment, the patient will not be followed up in the trial beyond that time point for further assessments of safety parameters.
Sample Size Determination	Based on published data, a very strong effect on the primary efficacy variable with a standardised effect size (Cohen‘s d) of at least 0.6 is expected, corresponding e.g. to a median reduction in wound area of 60% with a standard deviation of 100%. A sample size of 25 patients will have 80% power to detect a significant result with a 0.025 one-sided significance level under these assumptions. Given a possibly high drop-out rate and also some non progressing patients which will not be assigned to the efficacy analysis group, a total number of 40 patients will be recruited.
Statistical Analysis	The main statistical analysis of the primary and secondary efficacy parameters will be performed on the FAS using a pattern mixture model approach for missing data. As there will be no control group, optimistic assumptions about disease development for untreated patients will be used for the efficacy analysis. The primary efficacy variable percent reduction in the total wound area until V (24 weeks) will be analyzed with a One-sample Wilcoxon signed rank test.

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ALAT	Alanine Transferase
AP	Alkaline Phosphatase
ASAT	Aspartate Transferase
BSC	Best Supportive Care
CGI-I	Clinical Global Impressions-Improvement score
CGI-S	Clinical Global Impression-Severity scale
CKD	Chronic Kidney Disease
CRP	C-reactive protein
CTx	turn-over marker for bone resorption
CUA	Calcific Uremic Arteriolopathy
COMP	Committee of Orphan Medicinal Products
EC	Ethics Committee
eCRF	electronic Case Report Form
EMA	European Medicines Agency
ESRD	End Stage Renal Disease
ETHE1	Ethylmalonic Encephalopathy 1
FAS	Full Analysis Set
FFP	Fresh Frozen Plasma
GGT	Gamma-glutamyltransferase
HD	Hemodialysis
LOCF	Last Observation Carried Forward
MGP	Matrix GLA protein
pO_2	Oxygen Partial Pressure

PPS	Per-Protocol Set
PSUR	Periodic Safety Update Report
PTH	Parathyroid Hormone
pVO_2	Venous Oxygen Tension
SAP	Statistical Analysis Plan
SB	Standard Bicarbonate
SFU	Survival Follow Up
sO_2	Venous Oxygen Saturation of Hemoglobin
SQR	Sulfur-Quinone Oxidoreductase
STS	Sodium Thiosulfate
TS	Thiosulfate
TST	Thiosulfate Sulfurtransferase (= Rhodanese)
VAS	Visual Analogue Scale

1 INTRODUCTION AND BACKGROUND

1.1 Information on Calciphylaxis

Calciphylaxis, also known as calcific uremic arteriolopathy (CUA), is a rare but catastrophic disease which mainly affects patients with end stage renal disease (ESRD) and is associated with a 1-year mortality of 60-80% of the patients (Wilmer and Magro, 2002; Weenig, 2008; Schlieper et al., 2009; Rogers and Coates, 2010). Calciphylaxis is histologically characterized by the triad of calcification of the media, proliferation of the intima, and thrombosis of the lumen of small skin vessels. Clinically, these changes lead to progressive and very painful non-healing ischemic skin ulcerations typically at the lower extremities and/or the abdomen. Assuming an annual incidence of 1-2% among dialysis patients (Musso et al., 2009), (Fine and Zacharias, 2002), (Angelis et al., 1997), e.g. in Switzerland, an estimated 15 to 25 new cases of calciphylaxis are currently expected to occur per year.

Unfortunately, to date there are neither proven therapies available for calciphylaxis, nor is there an established animal model to study its pathophysiology and to test potential treatment modalities. Clinical factors often associated with calciphylaxis include ESRD, female gender, hyper- or hypoparathyroidism, obesity, hyperphosphatemia, hypercalcemia, and the use of vitamin K antagonists (Schlieper et al., 2009).

With the current pathophysiologic concept of heterogenous and ill-defined derangements of mineral metabolism, treatment is aimed at arresting the proposed driving forces of calcification of the medial layer of the small skin arterioles in the hope to stop or reverse disease progression.

1.2 Pathophysiology of calciphylaxis

The development of calciphylaxis can be considered a two-step process: the development of the vascular lesion and the development of tissue ischemia due to the vascular lesion, plus other clinical events (Hanke et al., 2010), as demonstrated in Figure 1.

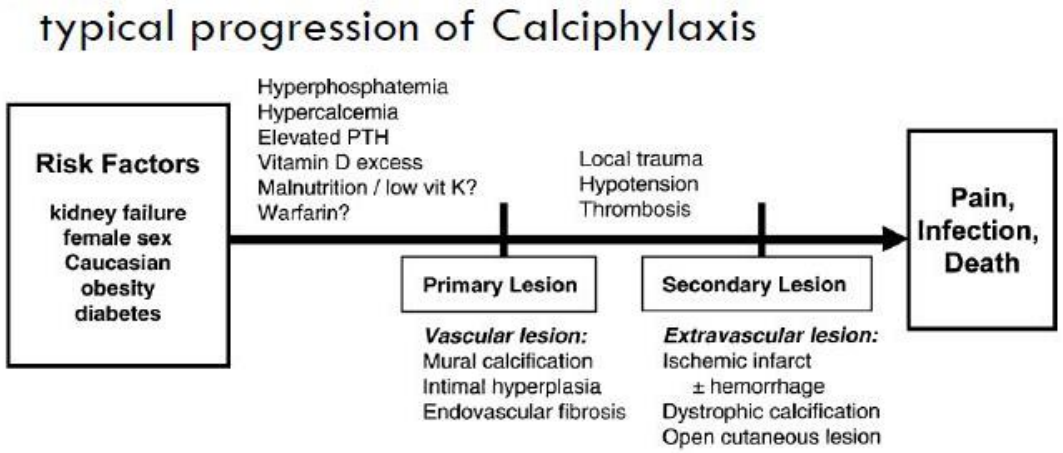

Figure 1: Development of calciphylaxis organ damage

Calciphylaxis affects skin arterioles in the subcutaneous tissue and leads to ischemic skin necroses, often clinically accompanied by opioid-resistant pain and non-healing ulcerations. Histologically, the skin lesions are characterized by medial calcification, endothelial proliferation and luminal thrombosis and are accompanied by a dramatic impairment of skin nutrition and ensuing skin (Brandenburg et al., 2011).

The order of occurrence of the histologic lesions and their potential role in the pathogenesis of calciphylaxis has not been clarified yet. Whereas it seems prudent to assume that the thrombotic occlusion of the vessel lumen is the final step in a cascade of events, it is not clear whether endothelial proliferation and medial calcification do occur concomitantly or sequentially, and if the latter was true – which comes first.

1.3 Conventional treatment options for calciphylaxis patients

Calciphylaxis patients represent by nature a very heterogeneous population with a broad range of calciphylaxis- associated and non-associated medications and diagnoses (as an estimate, the average dialysis patient has 10-15 diagnoses and is on 10-15 different drugs). No standard treatment options for calciphylaxis patients are available.

Treatment modalities, which have been tested so far, are highly variable and all without decisive improvements of the disease course. Amongst others, treatments comprise the cessation of vitamin K antagonists, calcium containing phosphate binders and vitamin D compounds, the lowering of serum phosphate and calcium levels, the use of calcimimetics and of bisphosphonates (Smith et al., 2012), (Veitch et al., 2014). Furthermore, intensified dialysis, meticulous wound care and skin grafting, and even parathyroidectomy have been tried but have not been shown to be convincingly effective (Weenig et al., 2007). The only treatment modality, which was related more constantly with improved pain and wound healing, is the application of hyperbaric oxygen treatment (Benedetto and Emhoff, 2000), (Dean and Werman, 1998) (Benedetto and Emhoff, 2000), which is, however, available in selected centers only.

Apart from these measures, treatment is mainly symptomatic with intensified wound care, and the liberal use of antibiotics and analgesics. Unfortunately, none of these measures alone or in combination has convincingly changed the course and prognosis of calciphylaxis.

1.4 Sodium thiosulfate (STS) for the treatment of calciphylaxis

Sodium Thiosulfate (STS, $Na_2S_2O_3$) is a sulfur salt, which has been used for decades in human medicine and was approved for (i) the treatment of cyanide intoxications (Miller and Toops, 1951) and (ii) as a chemoprotectant against cisplatin-induced oto- and nephrotoxicity (Gandara et al., 1990).

Besides these indications, STS has anecdotally been reported to prevent the progression of nephrocalcinosis (Agroyannis et al., 2001), metastatic calcifications (Papadakis et al., 1996), (Yatzidis, 1985), (Yatzidis and Agroyannis, 1987), kidney stones (Yatzidis, 1985), and coronary artery calcification (Adirekkiat et al., 2010).

In addition, based on theoretical considerations STS has been first used for the treatment of calciphylaxis back in 2004 (Cicone et al., 2004). Case reports in more than 280 patients are available indicating that STS might be beneficial for the treatment of calciphylaxis both in

improving the severe pain associated with the condition and in the healing of calciphylaxis lesions (Guerra et al., 2005), (Landau et al., 2007), (Mataic and Bastani, 2006), (Ackermann et al., 2007), (Zitt et al., 2013). Since then, STS has been used off-label for treatment of calciphylaxis but has also been investigated in open label, clinical studies for treatment of other calcifications (e.g. (Adirekkiat et al., 2010).

On 23 February 2011, orphan designation (EU/3/10/848) was granted by the European Medicines Agency (EMA) for sodium thiosulfate for the treatment of calciphylaxis (EMA-COMP, 2011).

The literature documenting the use of STS in the treatment of calciphylaxis is comprehensively reviewed by *Smith et al.*, along with a detailed summary of case reports and case series. Most of these reports documented treatment success, with rapid resolution of pain within days or weeks, often supported by impressive reductions in requirements for analgesia. Cessation of new lesion formation along with complete or partial wound healing or reduction in the size of subcutaneous plaques was also commonly reported. However, most reports described single cases or retrospective analyses of a small number of patients at dialysis centers (Smith et al., 2012), (Zitt et al., 2013), (Salmhofer et al., 2013).

Recently, a retrospective data collection on 172 calciphylaxis patients in centers in the USA over a period of 4 years was reported (Nigwekar et al., 2013). Of these, a complete survey was available for 53 calciphylaxis patients demonstrating substantial improvement in their symptoms. Among surveyed patients, calciphylaxis completely resolved in 26.4%, markedly improved in 18.9%, improved in 28.3%, and did not improve in 5.7% of the patients; in the remaining patients (20.8%), the response was unknown. One-year mortality in patients treated with STS was 35% compared to 60-80% without treatment (Weenig et al., 2007).

1.5 Mode of action of STS

The mode of action of STS is still not completely clarified, however, there are hypothetical models explaining the action of STS in vascular calcification in general, which may be extrapolated to its action in calciphylaxis.

STS appears to have pleiotropic pharmacodynamic properties which might explain its beneficial effects in the diverse spectrum of clinical applications mentioned above. When applied as an antidote in cases of cyanide intoxications, thiosulfate and cyanide are converted to the less toxic thiocyanate by the action of the mitochondrial enzyme thiosulfate sulfurtransferase (TST = rhodanese) (Hildebrandt and Grieshaber, 2008). In contrast, the detoxification of the chemotherapeutic cisplatin is accomplished by the formation of a thiosulfate-cisplatin complex, which prevents the entry of cisplatin into cells and probably facilitates its excretion from the body.

The calcification preventing and anti-ischemic properties of STS, which are probably effective in the treatment of calciphylaxis, may in contrast be due to the following mechanisms of action: (i) chelation/solubilization of calcium (O'Neill, 2008), (ii) induction of an anion gap acidosis (Cicone et al., 2004), (iii) anti-oxidative properties (Hayden and Goldsmith, 2010) (8), (iv) upregulation of calcification preventing proteins (e.g. Matrix GLA Protein [MGP] and fetuin-A) (Pasch et al., 2008), and (v) generation of H_2S, a potent vasodilator (Sen et al., 2008), (Hayden et al., 2008).

Hayden et al. 2005 have formed a hypothesis that the rapid reduction in pain may be due to a restoration of endothelial function associated with this syndrome. The antioxidant effect of STS, given in the i.v. dosing of 12.5–25 grams i.v. at the end of dialysis may help to restore the dysfunctional endothelial cell and begin restoring the endothelium's natural tendency (in health) to produce endothelial nitric oxide (eNO) promoting vasodilation instead of the damaging super oxide and the resultant peroxynitrite (Hayden et al., 2005).

STS may furthermore revert a functional vasoconstriction via the vasodilating molecule H_2S which is likely produced as a consequence of endogenous STS metabolism (Sen et al., 2008). The H_2S-induced dilatation of narrowed skin vessels could also explain the rapid reduction of the (presumably ischemic) pain, which is often seen after the start of STS therapy. The improved oxygen and nutrient supply would then - as in hyperbaric oxygen therapy – support the healing of the ulcerations.

In conclusion, the therapeutic effects of STS are probably mainly due to the neutralization of vasculature-harming reactive oxygen species and the – possibly coupled – generation of a potent vasodilator (H_2S).

The proposed mechanisms of action of STS might thus beneficially affect both, the medial calcifications and the vascular luminal narrowing. The potential of inhibition of calcium precipitation and calcium chelation is probably rather a contributing therapeutic effect of STS.

1.6 Pharmacokinetics

Thiosulfate (TS, $S_2O_3^{2-}$), the anion of STS, is an endogenous intermediate of mammalian sulfur metabolism. The endogenous synthesis of TS is accomplished by three mitochondrial enzymes, sulfur-quinone oxidoreductase (SQR), ethylmalonic encephalopathy 1 (ETHE1) and the TST enzyme (Hildebrandt and Grieshaber, 2008). The physiological excretion of TS is in the range of 10-20 µmol/day in the urine of healthy persons and depends on protein intake and likely on genetic factors (Farese et al., 2011).

Because of the free filtration of STS in the renal glomerulum, the negligible tubular handling, its low protein binding and the distribution in the extracellular space, STS was widely used as an alternative to inulin clearance measurement for the routine determination of kidney function in the 1940s to 1970s (Vorburger et al., 1969).

There are only few data on the pharmacokinetics in humans available in the literature.

In healthy volunteers, STS is poorly absorbed orally, but is rapidly distributed throughout extracellular fluid after i.v. administration. STS taken orally is not systemically absorbed. Most of the thiosulfate is oxidized to sulfate or is incorporated into endogenous sulphur compounds; a small proportion is excreted through the kidneys. Approximately 20-50% of exogenously administered STS is eliminated unchanged via the kidneys. The volume of distribution of STS is 150 mL/kg. STS is excreted in the urine, with a clearance half-life of 0.25 to 3 hours being reported when a single bolus dose of 1 g of STS is given. However, after an i.v. injection of a substantially higher dose of STS (150 mg/kg, that is, 9 g for 60 kg bw) in normal healthy men, the reported elimination half-life was 182 minutes (for details, see Investigator's Brochure).

In the absence of an intact kidney function (i.e. in dialysis patients) STS is completely metabolized endogenously and the resulting sulfate is largely removed during the next dialysis session (Farese et al., 2011). Therefore and because of a better tolerability, start of infusion of

STS is recommended 30 min before the end of hemodialysis (HD) with an overall infusion duration of 60 min.

1.7 Safety profile

STS has been used in human medicine for decades. In the 1950s and 1960s it was used for the determination of renal function. An assessment of the periodic safety update reports (PSUR) since the international birthdate of STS in 1978 in Germany did not reveal critical side effects such as acute poisoning, death or any deterioration of the patient that required admission to a hospital. This assessment includes data from 24 human studies comprising more than 1,200 patients who have been treated with STS as a cancer chemoprotectant primarily for the prevention of cisplatin-induced ototoxicity.

STS seems to have an acceptable safety profile and is usually well tolerated. The most prominent side effects reported with STS are nausea and vomiting, often in patients treated with a dose of 25 g 3x per week, and are usually described as mild, temporally related to the infusion, and responsive to antiemetics and/or prokinetics. Reducing the dose or rate of infusion can be helpful. A raised anion gap metabolic acidosis is also well recognized, and can be severe (Selk and Rodby, 2011; Mao et al., 2013). This is again less of a problem with a reduced dose, but is also relatively easily managed with bicarbonate supplementation or increasing the dialysate bicarbonate.

Headache, hypotension, thrombophlebitis (when STS is given through a peripheral i.v. cannula), and hypersensitivity to smells with anorexia have been reported (Baker et al., 2007), (Musso et al., 2009), (Ong and Coulson, 2011), (Tokashiki et al., 2006).

With regard to longer-term adverse effects, there is some concern regarding the possibility of bone demineralization, with a reduction in bone strength/bone mineral density (BMD) compared with controls reported in both animal and human studies of STS. *Adirekkiat et al.* demonstrated a significant reduction in total hip BMD and a trend towards a reduction in lumbar spine BMD in 15 patients treated with 12.5 g i.v. STS twice weekly for 4-months (Adirekkiat et al., 2010). This dose is within the dose range usually given for the treatment of calciphylaxis (6-25 g for 3x per week). The reason for the reduction in BMD is unclear, but the metabolic acidosis induced by STS treatment was proposed as a contributing factor. Another study in 22 haemodialysis patients could not detect any reduction in lumbar BMD after STS treatment for

5 months (Mathews et al., 2011). Although reports from the literature regarding bone-demineralisation effects of STS are contradictory, any bone fractures in longer-term survivors of calciphylaxis patients treated with STS should be observed and thoroughly monitored.

No other serious side effects have been reported despite the long clinical use of STS.

1.8 Animal proof-of-concept studies with sodium thiosulfate in calciphylaxis

No animal model of calciphylaxis is available. However, *Pasch et al.* used a rat model of renal failure based on addition of adenine to the diet, which produces severe interstitial nephritis and uremia, with medial vascular calcification developing within 4 weeks (Pasch et al., 2008). STS prevents calcification in this model at a dose and interval comparable to those used in humans with calciphylaxis/CUA, thus providing a scientific basis for its clinical use. This model of renal failure is associated with marked polyuria and salt wasting rather than oliguria and sodium retention in dialysis patients, which could differentially affect STS levels and calcium balance.

The authors determined whether it also prevents development of vascular calcifications in chronic kidney disease (CKD). They found inter alia that uremic rats treated by STS had no histological evidence of calcification in the aortic wall whereas almost three-fourths of untreated uremic rats showed aortic calcification. Urinary calcium excretion was elevated and the calcium content of aortic, heart and renal tissue was significantly reduced in the STS-treated compared to non-treated animals. STS treatment transiently lowered plasma ionized calcium and induced metabolic acidosis. It also lowered bone strength in the treated animals compared to their normal controls. Hence, STS prevented vascular calcifications in uremic rats, likely by enhancing acid- and/or chelation-induced urinary calcium loss (see also Investigator's Brochure).

As mentioned above, no animal model for calciphylaxis is available and therefore, the pathophysiology and histology of calciphylaxis need to be studied in human biopsies, in which calcifications can be detected. As no biopsy study has been conducted longitudinally in calciphylaxis so far, neither the putative role of media calcification nor the sequence of the occurence of the typical histologic lesions intimal proliferation, medial calcification and luminal thrombosis of the small skin vessels have been elucidated yet. Consequently, the questions whether calcification is the *primum movens* or a consequence of ischemic changes induced by intimal proliferation and luminal thrombosis awaits clarification.

2 RATIONALE

2.1 STS for the treatment of calciphylaxis

Up to now, no prospective clinical trial with STS has been performed. Reasons are that calciphylaxis is a rare condition and treatment is not focused on certain centres making feasibility studies nearly impossible. Due to the limited number of patients and the spontaneous occurrence of the disease, the recruitment of calciphylaxis patients is challenging.

The previous case reports on successful treatments of calciphylaxis patients with STS support the intention to demonstrate the efficacy and safety of STS in this patient population under the conditions of a prospectively planned clinical trial.

2.2 Rationale for the dose of STS

Studies on safety and efficacy of various STS doses and on the treatment duration of STS are not feasible in calciphylaxis due to the heterogeneity and paucity of patients.

The application of doses in the range of 12.5 to 25 g has been reported in most publications on calciphylaxis patients. This dose range is based on the experience with STS as antidote for cyanide poisoning and extravasation of chemotherapeutic agents.

Only few case reports are available on the treatment of cyanide poisoning. The dose range reported for these cases was 8-12.5 g or 0.2 g/kg bodyweight, administered as bolus injection or infusion. The treatment duration was up to 12 h.

For extravasation of chemotherapeutic agents (cisplatin), publications on more than 1200 patients are available with a dose range of 3-20 g/m^2 body surface area. Lower doses were infused over 3 to 15 min, higher doses were infused over several hours. The treatment duration was up to 12 h.

Case reports and cohort studies with more than 300 calciphylaxis patients have been published up to now (see also Investigator's Brochure). In the majority of reports, a dose of 25 g per day was used (see Investigator's Brochure, Table 14). Infusion occurred during 30-60 min at the end or after HD. Treatment duration was up to 62 weeks. On this basis, 25 g per day 3x per week was selected as an effective starting dose. To start with lower and potentially ineffective doses is ethically not acceptable for these patients. It was observed that flares may occur after reduction to 12.5 g or less, requiring subsequent increase of the STS dose to induce

improvement (Pasch, personal communication). Reduction of pain is considered a very good indicator of efficacy in calciphylaxis. Therefore, the individual dosing scheme was reported to often be adjusted based on pain response, which is usually achieved within two to three weeks after the first administration.

In the present clinical trial, the dose of 25 g will be administered i.v. as an infusion starting 30 min before end of HD over 60 min 3x per week. In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms.

In case of complete remission of the wound lesion after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4) the dose may only be reduced for safety reasons.

Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed.The change in dose is at the discretion of the investigator.

3 OBJECTIVE, STUDY DESIGN AND STUDY DURATION

The objective of this project is to study the potentially beneficial effects of STS on the course and outcome of calciphylaxis. The study population will consist of 40 patients ≥ 18 years of age with calciphylaxis. Patients will be treated with STS for at least 24 weeks. It is up to the discretion of the investigator to continue STS treatment.

The study design is a prospective, uncontrolled, multicenter, Phase 2/3 study including dialysis centers in 3 European countries (Switzerland, Germany, Austria).

The duration of the trial for each patient is expected to be up to 48 weeks plus the preceding 2 to 4 weeks run-in period.

The overall duration of the trial is expected to be approximately 4 years. The actual overall duration or recruitment may vary.

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint:

- Percent reduction of the total wound area after 24 weeks (V4) compared to baseline (V0) as assessed by 2 independent, blinded dermatologists using a serial photo documentation. The mean value of both assessments will be taken.

3.1.2 Secondary Endpoints:

- Status of skin lesions:
  - Total wound area at 8, 16, 36, 48 weeks compared to baseline (V0).
  - Complete remission of wound area.
  - Occurrence of new lesions: Time point of occurrence and – if applicable – healing as well as location of each lesion to be documented at each visit (V0 to V6).
  - Qualitative improvement of skin lesions at 8, 16, 24, 36, 48 weeks as assessed by the revised Photographic Wound Assessment Tool (revPWAT) score and evaluation of a serial photo documentation through 2 independent, blinded dermatologists.
  - Use of wound debridement
- Pain:
  - Reduction of pain in the areas of calciphylaxis after 4, 8, 16, 24, 36 and 48 weeks after start of STS treatment will be compared to baseline (V0) and

assessed by a visual analogue scale (VAS) for pain (0-10). This will be done directly before changing the wound dressing.
  - Consumption of pain medication (normalized to morphine equivalent with an appropriate conversion table) will be assessed at VR, V0 and 4, 8, 16, 24, 36 and 48 weeks after start of STS treatment and compared to baseline (V0).
- Clinical global impression:
  - Change in clinical global impression as assessed by the Clinical Global Impressions-Improvement (CGI-I) score at each follow-up visit (after 4, 8, 16, 24, 36 and 48 weeks) compared to baseline (V0) and the Clinical Global Impression-Severity scale (CGI-S) through the investigators. The Clinical Global Impression-Severity scale (CGI-S) will be assessed at each visit from visit V0 to V6 (i.e. after 4, 8, 16, 24, 36 and 48 weeks).
- Improvement leading to eligibility of the patient for kidney transplantation
  - Eligibility for kidney transplantation is given when the patient is being actively listed on a transplant waiting list.
- Bone mineral density (BMD)
  - For measurement of BMD, study sites will be evaluated for the availability of Dual Energy X-ray absorptiometry (DEXA) technique.
  - BMD will be measured at V0 and after 48 weeks (V6)
- Survival:
  - Median overall survival after start of STS treatment
  - One-year survival rate

3.1.3 Safety parameters:

- Adverse events
- AESI (incidence of infections and sepsis, metabolic acidosis, ventricular tachycardia, hypotension, bone fractures)
- Use of other concomitant medications
- Laboratory parameters (parathyroid hormone [PTH], total calcium, phosphorus, alkaline phosphatase, pH, CRP, leucocytes, hemoglobin, creatinine, albumin, Na, K, Cl, Mg, ASAT, ALAT, GGT, Amylase, Lipase, urea, uric acid, venous blood gas analysis, 1.25 vitamin D, 25 vitamin D, T50 test (in vitro blood test for calcification propensity by monitoring the maturation time (T50) of calciprotein particles in serum according to Pasch et al. (Pasch et al., 2012).
- Physical examinations, ECG, vital signs (heart rate, blood pressure)
- Tolerability of STS treatment
- Biobanking: collection of serum for assessing further relevant parameters, e.g. inflammatory and calcification parameters and bone turn-over markers. The evaluation of these parameters is planned to be performed within 5 years after the end of the trial.

3.2 Number of patients

We aim to include a total of 40 patients in this study. Recruitment and treatment of patients is planned to be performed in approximately 6 trial centers. Further sites might be selected during the active period of the trial.

3.3 Diagnosis

At start of the run-in phase (VR) and during the run-in phase, patients will be examined by serological and histological parameters as indicated to confirm the diagnosis of calciphylaxis and to exclude other causes for necrotizing skin lesions and ulcerations.

The following differential diagnoses should be considered depending on clinical circumstances:

- peripheral arterial occlusive disease
- vasculitis
- arterial embolism
- anti-phospholipid antibody syndrome
- coumarin necrosis
- cryoglobin-related skin disorder
- heparin necrosis
- nephrogenic systemic fibrosis

The following diseases and conditions have to be excluded histologically:

- Pyoderma gangraenosum
- coumarin necrosis
- nephrogenic systemic fibrosis

If the typical clinical signs for calciphylaxis are detected, in particular more than one lesion appears, and other diagnoses can be excluded based on the results of serological and histological analyses, the diagnosis of calciphylaxis can be confirmed.

3.4 Medications and measures for best supportive care

The following measures for best supportive care (BSC) are considered obligatory:

- Cautious necrosectomy only, no debridement of wound margins!
- Keep patients dry and treat peripheral edema to support wound healing

The following measures are considered as optional and are proposed in the literature as potential treatments for calciphylaxis patients. It is at the discretion of the trial centers respectively the investigators, which measures are appropriate for treatment during the run-in phase. However, all participating centers are free in their decision how to treat their calciphylaxis patients during the run-in phase:

- Reducing ionised Ca^{2+} and PO_4^- to the lower normal range
- Stopping vitamin D compounds (25-OH, 1,25-OH, paricalcitol)
- Replacement of calcium-containing phosphate binders
- Treatment of patients having hyperparathyreoidism with high bone turnover (high alkaline phosphatase) with parathyreoidectomy or Cinacalcet
- Stopping coumarine
- Replacing coumarine with low molecular weight heparins
- Administration of vitamin K
- Avoidance of iron therapy i.v./p.o.
- Reducing skin punctures and other tissue traumata to a minimum
- If applicable, surgical therapy /plastische cover of the lesion
- Permanent administration of antibiotics
- Avoidance of phosphate-containing enemas (contraindicated in patients with renal insufficiency)
- In case of peritoneal dialysis, switch to HD
- HD eKt/V at least 1.2
- Switch to HD during daytime or long nocturnal HD
- Switch to HDF
- Dialysis against low calcium dialysate (1.25 mmol/L or lower)
- Plasmapheresis against fresh frozen plasma (FFP)
- Hyperbaric oxygen

3.5 Study treatment

At start of the run-in phase (VR) of 2 to 4 weeks, patients will be treated with conventional medications and measures as described in section 3.4. Considering the severity of the disease, the run-in period has to be limited to 2 weeks for those patients rapidly progressing under BSC while for the other patients a 4-week run-in phase is justifiable.

If the investigator observes typical symptoms of calciphylaxis (e.g. pain, appearance of more than one wound lesion) and decides that the patient is eligible for the treatment with STS and participation in the clinical trial, a biopsy will be taken to confirm the diagnosis of calciphylaxis by excluding other causes of necroses and ulcerations. Patients with rapidly progressive disease under BSC will be allocated to Group A while patients with less progressive or initially stable disease will be allocated to Group B. Patients in both groups will be treated with STS. Both patient groups will be analysed separately, with Group A to establish efficacy and Group B to be assessed descriptively (see section 11.2.1). Patients with severe disease status may be switched to STS treatment earlier than 2 weeks. These patients will be excluded from the Per-Protocol (PP) analysis.

Then, at V0, treatment with STS starts and will be continued for at least 24 weeks. From the long-standing experience published in the literature, a clinically meaningful reduction (>20%) in the total wound area is expected by the clinical experts after 24 weeks of STS treatment.

The dose of 25 g will be administered i.v. as an infusion starting 30 min before end of HD over 60 min 3x per week. In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms.

In case of complete remission of the wound area after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4) the dose may only be reduced for safety reasons.

Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed. The total amount of STS administered over all treatments will be calculated and recorded for each visit.

It is at the discretion of the investigator to reduce the dose to a lower dose in case of adverse effects. Treatment will continue up to 48 weeks until either complete remission, reduction in pain, reduction in wound surface, healing of ulcera, or discontinuation due to side effects occurs.

3.6 Definition of treatment response

For patients treated with BSC, wound size is typically increasing as shown in the literature and medical expert knowledge. A median reduction of the total wound area of 20% or more is clearly a clinically relevant improvement as, again based on empirical medical knowledge, wound size is correlated with the detrimental symptoms of calciphylaxis. For the current study, a median wound size reduction of 50% or more is expected.

3.7 Safety Monitoring

Safety assessments start at the time point, when the patient enters the run-in phase (VR).

If the patient is excluded from the trial at baseline (V0) because the diagnosis of calciphylaxis cannot be confirmed or because the patient withdraws the consent for STS treatment, the patient will not be followed up in the trial beyond that time point for further assessments of safety parameters.

Safety parameters will include adverse events, concomitant pain and other medications, physical examinations, ECG, vital signs, standard clinical laboratory evaluations (as described in section 3.1.2), and tolerability of STS treatment.

4 PATIENT SELECTION

4.1 Inclusion Criteria

(1) All patients ≥ 18 years

(2) Male or female HD patients with a diagnosis of calciphylaxis. (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching).

(3) Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study

4.2 Exclusion Criteria

(1) Sodium metabisulfite hypersensitivity, among others the history of bronchial asthma due to known sodium metabisulfite hypersensitivity

(2) Pregnant or lactating patients. As pregnancy is an extremely rare event in HD patients, a pregnancy test will only be performed in ambiguous cases. (Of note, STS has been demonstrated not to cross the blood-placenta barrier in gravid eves (Graeme et al., 1999); therefore we regard fetal damage also as unlikely in humans).

(3) Patients who have participated in any other investigational studies within 30 days previous to enrollment

(4) History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment.

(5) Good response to conventional treatment.

(6) Life expectancy less than 4 months in the judgement of the investigator

4.3 Concomitant medications

All medications taken by the patients for treatment of the symptoms of calciphylaxis during the run-in phase and the subsequent STS treatment phase will be recorded in the eCRF with actual dose, duration of treatment and indication up to 48 weeks.

4.4 Patient Withdrawal

Patients are free to withdraw from the study at any time for any reason. In addition, patients may be withdrawn from the study by the Principal Investigator or Sub Investigator for the following reasons:

- Adverse events (e.g. uncontrollable infections, pain, nausea),
- progression despite treatment,
- severity of the disease

The clinical report will include reasons for patient withdrawals as well as details relevant to the patient withdrawal. If a patient is withdrawn from the trial prior to study completion, he/she will undergo all procedures scheduled for study completion.

4.5 Premature Closure of the Clinical Trial

The trial can be prematurely closed or suspended by the Coordinating Investigator or the sponsor in case that new risks for patients become known. The Ethics Committee (EC) and the competent regulatory authorities must then be informed. Furthermore, the Ethics Committee(s) and competent regulatory authorities themselves may decide to stop or suspend the trial.

Should the trial be closed prematurely, all trial material (investigational medicinal products, etc.) must be returned to the Sponsor.

All involved investigators have to be informed immediately about a cessation/ suspension of the trial. The decision is binding to all trial center's and investigators.

4.6 Treatment Assignment

The trial medication will be administered only to patients included in this trial.

Patients withdrawn from the trial retain their identification codes. New patients must always be allocated a new identification code.

4.7 Dosing of the study medication

At start of the run-in phase (VR) of 2 to 4 weeks, patients will be treated with conventional medications and measures as BSC (see section 3.4). If the investigator observes typical symptoms of calciphylaxis (e.g. pain, appearance of more than one wound lesion) and decides that the patients is eligible for the treatment with STS and participation in the clinical trial, a biopsy will be taken to confirm the diagnosis of calciphylaxis by excluding other causes of necroses and ulcerations. Then, patients will be treated with STS (V0).

The dose of 25 g will be administered i.v. as an infusion starting 30 min before end of HD over 60 min 3x per week. In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms.

In case of complete remission of the wound lesion after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4) the dose may only be reduced for safety reasons.

Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed in the eCRF.

It is at the discretion of the physician to reduce the dose to the next-lower dose in case of adverse effects.

Treatment will continue up to 48 weeks (V6) until either complete remission, reduction in pain, reduction in wound surface, healing of ulcera, or discontinuation due to side effects occurs.

4.8 Packaging and Labelling

The trial medication will be labelled according to GCP requirements.

4.9 Supplies and Accountability

The investigator will keep an account of the trial medication and acknowledge the receipt of all shipments of the trial medication.

The investigator will also keep accurate records of the quantities of trial medication used for each patient. The documentation has to include date of application, patient identification, batch/

serial numbers or other identification of trial medication. The site monitor will periodically check the supplies of trial medication held by the investigator to ensure the correct accountability of all trial medication used. At the end of the trial, all unused trial medication and all medication containers will be completely returned to the sponsor. It will be assured that a final report of the drug accountability is prepared and maintained by the investigator.

5 CONDUCT OF THE TRIAL AND STUDY ASSESSMENT SCHEDULE

The study shall be performed according to the following chronological steps, which are depicted hereafter and in Figure 1 and Flow Chart (Table 1).

5.1 Identification and inclusion of a calciphylaxis patient in the trial center

Patients with calciphylaxis are typically identified in dialysis centers.

A first diagnosis of suspected calciphylaxis will be performed according to the typical signs and symptoms (severe pain, livedo, violaceous plaques, ulcerations, necroses) and by excluding other causes of necroses and ulcerations as described in section 3.3.

Each patient will be identified by a 7-digit patient number, which is a combination of the 2-digit county number, the 2-digit site number and a unique 3-digit number. The country number (eg 01, 02 etc.) and site number (eg 01, 02 etc.) will be assigned by the CRO, the unique 3-digit number will be assigned to the patient by the investigator, starting with 001. For example, the patient number for the first patient in country 01 at site 01 will be 01-01-001.

At start of the 2 to 4-week run-in phase (VR), the patient will be informed about the character and individual consequences of the clinical trial and has to provide written informed consent to participate in the study.

Upon decision of eligibility of the patient to participate in this clinical trial by fulfilling all inclusion and no exclusion criteria, the diagnosis, medical history and demographic data, including sex, age, race, body weight (kg), height (cm), BMI and tobacco use will be recorded in the eCRF. Each patient will have a physical examination, vital sign measurements (heart rate, blood pressure, ECG), and the laboratory tests. Then, the patient will be treated with conventional medications and measures (see section 3.4).

If the investigator assesses the patients as eligible for the treatment with STS, a biopsy will be taken and analyzed during the run-in phase to confirm the diagnosis of calciphylaxis by excluding other causes of necroses and ulcerations. Additionally at the end of the study all biopsy samples will be analyzed centrally.

When the diagnosis of calciphylaxis has been confirmed, the patient will be asked again if he/she agrees to participate in the clinical trial and to undergo STS treatment.

The run-in phase will end on the same day, when patients will start treatment with STS (baseline, V0).

5.2 Photo documentation and assessment of the wound area

Photo documentation of all skin lesions (total wound area) will be performed at VR, V0 (baseline), V2 (8 weeks), V3 (16 weeks), V4 (24 weeks), V5 (36 weeks) and V6 (48 weeks, end of study) to follow progression as well as remission. A graded straight edge including a colored scale will be added at the edge of the wound. The photographs will be taken under common circumstances in the in-and outpatient departments without any additional light sources; flash light should be avoided if possible. On the photographs, the necrosis/ulcers and the surrounding skin will be included.

To avoid possible bias in the assessment of the wound area, it is important to choose a camera position perpendicular to the approximate center of the wound. The distance between camera and wound should be about 50 centimeters. This distance should not even be decreased for small wounds as smaller distances lead to image distortions especially if the wounds are located on curved surfaces. Instead, the zoom of the camera should be used as it does not create this type of distortions.

Nevertheless, wounds on strongly curved surfaces (arms, etc.) may not fit one photograph. In this case, several images of the same wound should be taken. To allow the later area assessment, pencil marks (for example small arrows) should be placed on the healthy skin at the border on the wound before the photographs are taken to denote, which part of the wound gets measured on image 1 and which on image 2.

For the measurement of the skin lesion, the inner edge of the wound will be taken. The area of each lesion will then be analyzed using the software package ImageJ.

An example is provided in Figure 2 demonstrating the assessment of the wound area in a calciphylaxis patient at start of STS treatment (calculated area is 68.6 cm^2).

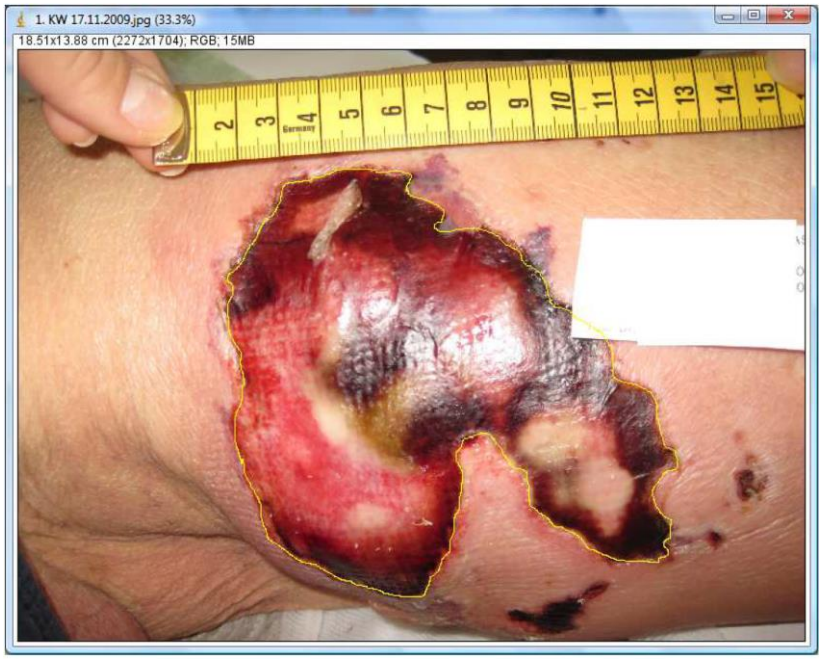

Figure 2: Photograpic documentation and assessment of wound area with the ImageJ software at start of STS administration in calciphylaxis patients

Changes in the appearance of the wounds will be assessed on the photographs by the blinded dermatologists using the revPWAT score (Thompson et al., 2013). This validated score consists of 8 domains with possible scores ranging between 0 and 32, with zero representing a completely healed wound (Figure 3). In case of missing efficacy scores (e.g. patient passes away or withdraws from the trial at later time points), the missing values will be imputed as described in 11.2.4 and the patient will be included in the efficacy analysis.

Figure 3: Photographic Wound Assessment Tool – revised (revPWAT)

Item	Assessment	Score
1. Size	0 = wound is closed (skin intact) or nearly closed (<0.3 cm^2) 1 = 0.5 – 2.0 cm^2 2 = 2.0 – 10.0 cm^2 3 = 10.0 – 20.0 cm^2 4 = > 20.0 cm^2	
2. Depth	0 = wound is healed (skin intact) or nearly closed (<0.3 cm^2) 1 = full thickness 2 = unable to judge because majority of wound base is covered by yellow/black eschar 3 = full thickness involving underlying tissue layers 4 = tendon joint capsule visible/bone present in wound base	
3. Necrotic tissue type	0 = none visible or wound is closed (skin intact) or nearly closed (<0.3 cm^2) 1 = majority of necrotic tissue is thin white/gray or yellow slough 2 = majority of necrotic tissue is thick, adherent white yellow slough or fibrin 3 = majority of necrotic tissue is white/grey devitalized tissue or eschar 4 = majority of necrotic tissue is hard grey to black eschar	
4. Total amount of necrotic tissue	0 = none visible in open wound or wound is closed (skin intact) or nearly closed (0.3 cm^2) 1 = < 25% of wound bed covered 2 = 25% to 50% of wound covered 3 = > 50% and < 75% of wound covered 4 = 75% to 100% of wound covered	
5. Granulation tissue type	0 = wound is closed (skin intact) or very close to closed (<0.3 cm^2) 1 = majority (>50%) of granulation tissue is healthy looking (even, bright red appearance) 2 = majority of granulation tissue is unhealthy (eg, pale, dull, dusky, hypergranulation) 3 = majority of granulation tissue is damaged, friable, degrading 4 = there is no granulation tissue present in the base of the open wound (all necrotic)	

Figure 3: continued

6. Total amount of granulation tissue	0 = Wound is closed (skin intact) or very close to closed (<0.3 cm^2) 1 = 75% to 100% of open wound is covered with granulation tissue 2 = >50% and <75% of open wound is covered with granulation tissue 3 = 25% to 50% of wound bed is covered with granulation tissue 4 = <25% of wound bed is covered with granulation tissue			
7. Edges (directly touching and within 0.5 cm of wound edge)	0 = Wound is closed (skin intact) or very close to closed (<0.3 cm^2) or edges are indistinct, diffuse, not clearly visible because of re-epithelialization 1 = majority of edges (>50%) are attached with an advancing border of epithelium 2 = majority of edges (>50%) are attached even with wound base (not advancing) 3 = majority of edges(>50%) are unattached and/or undermined 4 = majority of edges are rolled, thickened or fibrotic (do not include callus formation)			
8. Periulcer skin viability (consider skin visible in photo or within 10 cm of wound edge)	Number of factors affected 0 = None 1 = One only 2 = 2 or 3 3 = 4 or 5 4 = 6 or more	• callus • dermatitis • maceration • desiccation or cracking • bright red erythemic	• edema • excoriation • skin tearing/irritation related to wound dressing or tape • hypo-/hyperpigmentation • other: _____	
Total score				

5.3 Biopsy taking and histological assessment

A biopsy will be taken a few days before the end of the run-in phase to confirm the diagnosis of calciphylaxis by excluding other causes for necroses and ulcerations.

Spindle shapes skin biopsies will be taken in the participating centers by excision of an approximately 2 x 0.6 cm spindle-shaped piece of skin, radially involving healthy and calcified plaque-like skin, or healthy skin and the border of an ulcerative lesion.

Alternatively, a deep 5 mm punch biopsy will be taken from the border of the affected skin area. The biopsy wound can thereafter stay open or should be closed by a surgical suture, depending on heaviness of bleeding.

The biopsy will be analyzed by Alzain and Kossa stainings to detect calcification and thus, to confirm the condition of calciphylaxis or for exclusion of other causes of necrosis and/or ulceration of the skin.

5.4 Assessment of Bone Mineral Density (BMD)

The contract research organisation (CRO) performing the initiation of the study sites and monitoring for the clinical trial will evaluate the availability of DEXA scanners and the possibility to use this technique for determining the BMD in calciphylaxis patients at baseline (V0) and after 48 weeks (V6).

Dual **E**nergy **X**-ray **A**bsortiometry, or DEXA scanning, is currently the most widely used method and the most reliable technique for measurement of bone mineral density (BMD) for several reasons. DEXA is the clinical standard for measurement of BMD. DEXA scanners use an X-ray rather than gamma ray source to emit dual energy photons. The advantages of this technique are shorter scan time, lower radiation exposure (less than 3 mRem), higher precision and less expensive. DEXA scanning is more sensitive and accurate at measuring subtle changes in bone density over time or in response to drug therapy than is Qualitative computed tomography (QCT).

For the test, a patient lies down on an examining table, and the scanner rapidly directs x-ray energy from two different sources towards the bone being examined in an alternating fashion at a set frequency. BMD will be measured in the hip and spine. In certain situations – e.g. if the hip or spine cannot be measured - BMD will be measured in the forearm. The mineral density of the patient's bone weakens, or prolongs the transmission of these two sources of x-ray energy through a filter onto a counter in a degree related to the amount of bone mass present. The greater the bone mineral density, the greater the signal picked up by the photon counter. The use of the two different x-ray energy sources rather than more traditional radioisotope studies (such that would be used for a bone scan) greatly improves the precision and accuracy of the measurements.

5.5 Administration of STS

Upon confirmation of the condition of calciphylaxis by analysis of the biopsy, STS will be administered i.v. as an infusion over 60 min 3x per week by starting 30 min before end of HD at V0 (baseline).

In case of continued low tolerability of the STS high dose, it may be reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS has been achieved, the dose should be increased again to 25 g to avoid flares and recurrence of symptoms.

In case of complete remission of the wound lesion after at least 24 weeks of STS treatment, the dose may be reduced for the remainder of the study to 18.75 g or if appropriate, further lowered to 12.5 g. However, before week 24 (V4), the dose may only be reduced for safety reasons.

Time points of and reasons for any dose reduction or cessation of STS treatment will be assessed in the eCRF.

The association of the total amount of administered study drug and the treatment effect will be plotted and analyzed using a linear regression model.

5.6 Documentation of pain on a visual analogue-pain scale

Degree of pain will be assessed at start of the run-in phase (VR), at baseline (V0), and directly before changing wound dressings at 4 (V1), 8 (V2), 16 (V3), 24 (V4), 36 (V5) and 48 weeks (V6). The patient has to indicate his/her experience of present pain in the area of the wound lesions on a visual analogue scale (VAS) (0-10, i.e. no pain (=0) to worst pain imaginable (=10)).

A 10-20% decrease in pain intensity is considered minimally important, at least 30% decrease is moderately important, and more than 50% decrease is a substantial improvement (Breivik et al., 2008).

5.7 Documentation of pain medication and other concomitant medications

All participating centers are – apart from the study medication – free in their decision how to treat their calciphylaxis patients. This means that all therapeutic measures can be applied according to BSC at the participating center. These measures including concomitant medications have to be documented in the eCRF at each dialysis visit before start of dialysis.

Consumption of pain medication will be normalized to morphine equivalent with an appropriate conversion table and will be assessed at each visit, at which the VAS will be assessed (VR, V0 and after 4, 8, 16, 24, 36 and 48 weeks).

5.8 Treatment success/change in clinical global impression

After 24 weeks (V4), appraisal of therapy success will be assessed by photo documentation of the wound status, measurement of total wound area, and assessment of pain, as indicated in Section 3.1.1 primary endpoints.

- The changes in the clinical global impression will be assessed by the Clinical Global Impression-Severity scale (CGI-S) and the Clinical Global Impressions-Improvement (CGI-I) score according to Busner and Targum (Busner and Targum, 2007). The CGI-S rates the severity of the patient's illness at the time of assessment, the CGI-I allows to quantify and track patient progress and treatment response over time. The CGI-Sscale will be assessed for the first time at baseline (V0). TheCGI-I will then be assessed at each follow-up visit (V1-V6) and will be compared to baseline CGI-S. The Clinical Global Impression-Severity scale (CGI-S) will be assessed at each visit from visit V0 to V6. The following query is rated on a seven-point scale:

“Considering your total clinical experience with this particular population, how ill is the patient at this time:

1= normal, not at all ill;

2=borderline mentally ill

3=mildly ill;

4=moderately ill;

5= markedly ill;

6=severely ill;

7=extremely ill."

"Compared to the patient's condition at the baseline visit (V0), this patient's condition is:

1=very much improved since the initiation of treatment;

2=much improved;

3=minimally improved;

4=no change from baseline (the initiation of treatment);

5=minimally worse;

6= much worse;

7=very much worse since the initiation of treatment."

5.9 Eligibility of the patients for kidney transplantation

Eligibility for kidney transplantation is given when the patient is being actively listed on a transplant waiting list.

5.10 Occurrence of new lesions

The time point of occurrence and – if applicable – healing as well as the location of eachlesion will be documented in the eCRF. In order to ensure traceability of the lesions each lesion will receive at time of occurrence a consecutive number (L1 to LX) which will be maintained throughout the study.

5.11 Follow-up period up to 48 weeks

If tolerated by the patient, the dose of 25 g 3 x per week should be applied up to 24 weeks (V4) to assess the efficacy of this dose for the primary endpoint. During the continuing period up to 48 weeks, either continuation or slow reduction of STS dosing may occur as needed by the patient or in case of complete wound healing after at least 24 weeks of treatment. If cessation of STS is decided by the investigator for safety reasons (allowed at any time) or because of complete wound healing (only allowed after 24 weeks of treatment), a restart of STS treatment

is possible in case of flares and recurrence of symptoms. Each change in dosing, stop of administration of STS and restart of STS treatment has to be recorded in the eCRF.

5.12 Laboratory parameters

At start of the run-in phase (VR), at baseline (V0), and after 8, 16, 24 and 48 weeks, blood sampling and freezing of a 10 ml serum vial directly before dialysis has to be performed for analysis of laboratory parameters (PTH, total calcium, phosphorus, alkaline phosphatase, pH, CRP, leucocytes, hemoglobin, creatinine, albumin, Na, K, Cl, Mg, ASAT, ALAT, GGT, Amylase, Lipase, urea, uric acid, venous blood gas analysis (pH, pO_2, pVO_2, sO_2, SB), 1.25 vitamin D, 25 vitamin D). Analysis of these blood parameters will be performed locally at the respective study site.

The T50 test will be conducted to obtain information on the calcification propensity by monitoring the maturation time (T50) of calciprotein particles in serum (Pasch et al., 2012). For this test, about 2 ml blood samples (serum) will be taken at the respective time points (VR, at baseline (V0), and after 8, 16, 24 and 48 weeks). Labelled tubes will be provided to the study site by the central laboratory. The analysis of the samples will be done within 5 years after end of study by the company Calcisco AG, Switzerland. Remaining samples will be destroyed at the Calcisco AG.

For establishing a biobank for calciphylaxis, blood samples (serum) will be analyzed for relevant parameters, e.g. inflammatory and calcification parameters and bone turn-over markers At each time point of blood sampling (see above), additionally 10 ml serum will be taken. Labelled tubes will be provided to the study site by the central laboratory..

All samples will be shipped on dry ice to the central laboratory on the day of collection and are stored centrally at -80°C until analysis will be performed.

5.13 Soft tissue radiographs - optional

It is optional, i.e. at the discretion of the investigator to take soft tissue radiographs using mammography x-ray technique at baseline (V0) to assess the status of soft tissue calcifications in the areas of the skin lesions.

5.14 Safety Monitoring

Several adverse events, which may occur during the course of the study, are caused by the underlying and often long-lasting disease/condition of calciphylaxis patients.

Adverse events (AEs) will therefore be entered into the eCRF, if they are evaluated as new symptom/medical condition, as AE of special interest (AESI), new diagnosis, changes of laboratory parameters, intercurrent diseases and accidents, recurrence of disease, increase of frequency or intensity of episodical diseases, according to the definition of AEs in section 7.1.1. However, all serious AEs (SAEs) need to be recorded in the eCRF. All patients will be followed for AEs and SAEs for 7 days following the last dose of STS.

Details of assessment and reporting of adverse events are presented in Section 7.

5.15 Study Flow Chart

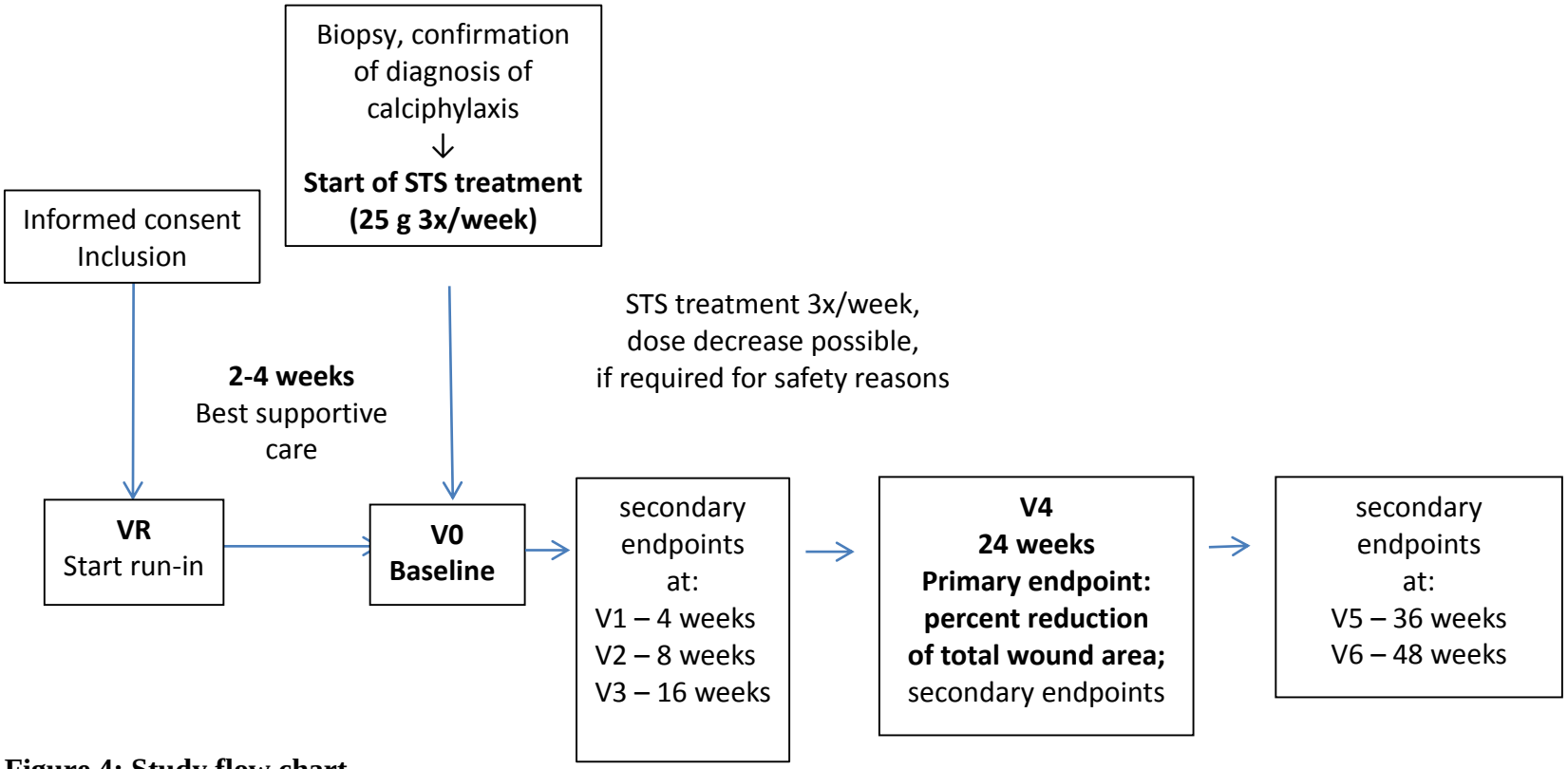

Figure 4: Study flow chart

Table 1: Flow Chart

	Screening	VR Start of run-in phase; duration of 2 to 4 weeks	V0 end of run-in = baseline	V1 4 weeks	V2 8 weeks	V3 16 weeks	V4 24 weeks	V5 36 weeks	V6 48 weeks	SFU 1 0.5 year after treatment	SFU 2 1 year after treatment
Informed consent of the patient	X		X								
Physical examination, vital signs, ECG[1]		X	X	X	X	X	X	X	X		
Inclusion and exclusion criteria,	X		X								
Demographics, baseline characteristics		X									
Skin biopsy for diagnosis of calciphylaxis			X[2]								
Soft tissue radiographs (optional)			(X)								
Documentation of total wound area (photograph and calculation of wound size)		X	X		X	X	X	X	X		

[1] ECG only during physical examination at start of run-in phase

[2] If patient is assessed by the investigator as eligible for STS treatment

SFU – survival follow-up

	Screening	VR Start of run-in phase; duration of 2 to 4 weeks	V0 end of run-in = baseline	V1 4 weeks	V2 8 weeks	V3 16 weeks	V4 24 weeks	V5 36 weeks	V6 48 weeks	SFU 1 0.5 year after treatment	SFU 2 1 year after treatment
revPWAT score		X	X		X	X	X	X	X		
Laboratory parameters (including samples for biobanking)		X	X		X	X	X		X		
VAS for pain (0-10)[3]		X	X	X	X	X	X	X	X		
Pain medication requirement		X	X	X	X	X	X	X	X		
Other concomitant medication/measures (e.g. wound debridement)		X	X	X	X	X	X	X	X		
CGI-I				X	X	X	X	X	X		
CGI-S			X	X	X	X	X	X	X		
Occurrence of new lesions under STS treatment				X	X	X	X	X	X		
BMD (optional)			X						X		
Adverse events		X	X	X	X	X	X	X	X		
Survival rate										X	X

[3] VAS for pain will be assessed directly before change of wound dressing.

6 PLAN FOR TREATMENT OR CARE AFTER THE TRIAL

Patients, who will need further treatment after the end of this clinical trial, will be treated according to current BSC at the respective study site.

Follow-up telephone interviews with the investigators 0.5 and 1 year after the end of the trial are planned (disease status, continuation of STS-treatment, survival, further/additional treatment and new medication for treatment of calciphylaxis).

7 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE may be:

- New symptom/ medical condition,
- New diagnosis,
- Changes of laboratory parameters,
- Intercurrent diseases and accidents,
- Recurrence of disease,
- Increase of frequency or intensity of episodical diseases.

A pre-existing disease or symptom will not be considered an adverse event unless there will be an untoward change in its intensity, frequency or quality. This change will be documented by an investigator.

All AEs (inclusive SAEs) will be documented on an electronic AE-form. AEs are classified as "non-serious" or "serious".

7.1.2 Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) are those events thought to be (potentially) associated with the investigational compound or disease under study. Despite treatment with BSC in the run-in phase or with STS in the study period, calciphylaxis lesions may progress leading to infections, sepsis and potentially to death. Cases were reported where sepsis in calciphylaxis patients under STS treatment led to death (Norris et al., 2005), (Mataic and Bastani, 2006), (Auriemma et al., 2011). Therefore, infections and sepsis will be assessed as AESIs.

Other AESIs potentially related to STS are the occurrence of metabolic acidosis (Zitt et al., 2013), ventricular tachycardia (Amin et al., 2010), hypotension (Nigwekar et al., 2013), and bone fractures (Adirekkiat et al., 2010). More information about these adverse events is provided in the Investigator's Brochure (IB).

7.1.3 Serious Adverse Event

A serious adverse event (SAE) is one that at any dose (also overdose):

- Results in death,
- Is life-threatening (the term life-threatening refers to an event in which the patient was at risk of death at the time of event and not to an event which hypothetically might have caused death if it was more severe),
- Requires patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/ incapacity,
- Is a congenital anomaly/ birth defect.

All SAE will additionally be documented on an electronic SAE-form.

7.1.4 Expectedness

An 'unexpected' adverse event is one the nature or severity of which is not consistent with the applicable product information, e.g. Investigators Brochure. Furthermore, reports which add

significant information on specificity or severity of a known adverse reaction constitute 'unexpected' events.

7.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SAEs that are both suspected, i.e. possibly related to the IMP and 'unexpected', i.e. the nature and/ or severity of which is not consistent with the applicable product information (IB or SmPC) are to be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs).

In case, either the investigator who primary reported the SAE or the second assessor classify the SAE as 'suspected', i.e. related to the IMP and the SAE is 'unexpected' it will be categorized as a SUSAR.

All SUSARs are subject to an expedited reporting to the responsible ethics committee(s), the competent higher federal authority and to all participating investigators.

7.2 Period of Observation and Documentation

AEs will be documented from a time of the study inclusion up to end of the study up to 48 weeks. All patients who present AEs, whether considered associated with the use of the trial medication or not, will be monitored by the responsible investigator to determine their outcome. The clinical course of the AE will be followed up until resolution/normalization of changed (laboratory) parameter or until it has changed to a stable condition.

Each AE has to be classified in respect to the following five characteristics:

7.2.1 Intensity of the AE

The classification of intensity in this trial will be carried out on the basis of a 3-grade scale as follows:

Mild: signs and symptoms which can be easily tolerated. Symptoms can be ignored or disappear when the patient is distracted.

Moderate: symptoms cause discomfort but are tolerable, they cannot be ignored and affect normal activity.

Severe: symptoms strongly affect normal activity.

7.2.2 Relatedness of the AE to the IMP

The investigator will evaluate each AE that occurred after patient's study inclusion regarding the coherency with the administration of the investigational medicinal product. There will be following criteria for classification in respect to the relatedness to the IMP:

'related':	There is a reasonable possibility that the event may have been caused by IMP. A certain event has a **strong temporal relationship** and an alternative cause is unlikely.
'probable':	An AE that has a reasonable possibility that the event is likely to have been caused by IMP. The AE has a **timely relationship** and **follows a known pattern of response**, but a potential alternative cause may be present.
'possible':	An AE that has a reasonable possibility that the event may have been caused by IMP. The AE has a **timely relationship** to the IMP; **however, the pattern of response is untypical**, and an alternative cause seems more likely, or there is significant uncertainty about the cause of the event.
'unlikely':	Only a remote connection exists between the IMP and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event.
'not related':	An AE that does not follow a reasonable temporal sequence related to the IMP and is likely to have been produced by the patient's clinical state, other modes of therapy or other known etiology.
'not assessable':	The relationship between an AE and the IMP that does not follow a reasonable temporal sequence from trial participation and that is likely to have been produced by the patient's clinical state, other modes of therapy or other known etiology.

7.2.3 Outcome of the AE

The outcome of an AE at the time of the last observation will be classified as:

‘Recovered/ resolved’:

all signs and symptoms of an AE disappeared without any sequel at the time of the last interrogation,

‘Recovering/ resolving’:

the intensity of signs and symptoms has been diminishing and/ or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution,

‘Not recovered/ not resolved’:

signs and symptoms of an AE are mostly unchanged at the time of the last interrogation,

‘Recovered/ resolved with sequelae:

actual signs and symptoms of an AE disappeared but there are sequelae related to the AE,

‘Fatal’: resulting in death. If there are more than one adverse event only the adverse event leading to death (possibly related) will be characterized as ‘fatal‘,

‘Unknown’: the outcome is unknown or implausible and the information cannot be supplemented or verified.

7.2.4 Action taken with the IMP

The action taken with IMP will be assigned to one of the following categories:

‘Dose not changed’: no change in the dose of IMP,

‘Dose reduced’: reduction in the dose of IMP,

‘Dose increased’: increase in the dose of IMP,

‘Drug withdrawn’: discontinuation of IMP,

‘Unknown’: the information is unknown or implausible and it cannot be supplemented or verified,

'Not applicable': the question is implausible (e.g. the patient is dead).

7.2.5 Countermeasures

The term 'Countermeasures' refers to the specific actions taken to treat or alleviate adverse events or to avoid their sequelae. Following categories will be used to categorize the countermeasures to adverse events:

'None': no action taken,

'Drug treatment': newly-prescribed medication or change in dose of a medication,

'Others': other countermeasures, e.g. an operative procedure.

7.3 Reporting of Serious Adverse Events by Investigator

All SAEs must be reported by the investigator to the responsible medical monitor of the CRO within 24 hours after the SAE becomes known using the "Serious Adverse Event" form.

Any SAE should be reported to

Name	Assign Safety Desk
Fax	+43 (0) 512 281514
Phone	+43 (0) 676 844033835
E-mail	SafetyDesk@assigngroup.com

The initial report must be as complete as possible including details of the current illness and (serious) adverse event and an assessment of the causal relationship between the event and the trial medication.

7.4 Expedited Reporting

SUSARs are to be reported to the ethics committee(s), competent higher federal authority and to all participating investigators within regulative defined timelines, i.e. they are subject to an expedited reporting.

Investigators participating in this trial will report all SUSARS to Assign Safety Desk as soon as possible but not later than 24 hours after their notification. The reporting will be performed by faxing of a completed 'SAE Form'.

A second assessment and expedited reporting to ethics committee(s) and regulatory agencies will be performed by the sponsor and Assign Safety Desk; details and responsibilities of these pharmacovigilance activities will be defined in a Safety Management plan.

7.5 Emergency Unblinding

not applicable.

7.6 Emergency Treatment

During and following a patient's participation in the trial, the investigator will ensure that adequate medical care is provided to a patient for any AE, if required. The investigator will inform a patient when medical care is needed for intercurrent illness of which the investigator became aware.

8 DATA MANAGEMENT

8.1 Data collection and handling

All protocol-required information collected during the trial must be entered by the investigator, or a designated representative, in the eCRF. Patient data will be documented pseudonymously. The investigator, or a designated representative, should complete the eCRF pages as soon as possible after the information is collected, preferably on the same day when a patient is seen for an examination, treatment, or any other trial procedure. Any pending entries must be completed immediately after the final examination. Explanation should be given for all missing data.

The CRO will check completeness, validity and plausibility of data by validating programs, which will generate queries. The investigator or the designated representative is obliged to clarify or explain the queries. The data management is accomplished with the appropriate SOPs valid.

8.2 Electronic Case Report Forms (eCRF)

The case report form represents a faithful reflection of the trial plan requirements.

All data required by the protocol will be carefully and uninterruptedly recorded in the eCRF. eCRF entries and corrections will only be performed by study site staff authorized by the investigator. Each user is informed by the CRO of the clinical study web-site internet address and is allocated to a user account with a personal password to access the confidential web site. The personal password must be kept confidentially and must only be used by the person to whom it was assigned. For additional authorized users at the site, a new user account needs to be requested to ensure that each entry/change can be allocated to the person who performed the entry/change. All visit data need to be recorded in the database as soon as possible after each visit.

Corrections may be requested as follows:

- Investigators' responses are checked as they are entered and are rejected if they do not fulfill quality criteria. A message will specify the type of error and assist in its correction.
- If required, the CRA can ask for information to be corrected during monitoring.
- Computerized data-check programs and manual checks will identify clinical data discrepancies for resolution. Corresponding queries will be created within the system and the site will be informed about new issues to be resolved on-line.

All discrepancies will be solved on-line directly by the investigator or by authorized staff.

8.3 Storage and archiving of data

All important trial documents will be archived by the sponsor for at least 10 years after the trial termination.

The investigator(s) will archive all trial data (source data and Investigator Site File (ISF) including patient identification list and relevant correspondence;) according to the section 4.9 of the ICH Consolidated Guideline on GCP (E6) and to local law or regulations.

9 STUDY MONITORING

9.1 Monitoring

The study will be performed in accordance with Good Clinical Practice and will thus require regular monitoring visits. Monitoring will be done by personal visits from a clinical monitor. Monitoring visits will occur based on patient accruals and availability of entries into the eCRFs. The monitor will review the entries into the eCRFs on the basis of source documents. Details of monitoring (i.e. frequency of visits and/or extent of Source Data Verification (SDV)) will be specified in the monitoring manual for this trial. Between these visits, contacts with study site personnel will be made by telephone, by fax or by mail, to ensure that the trial is conducted according to the protocol and the regulatory requirements.

Prior to the monitor's visit, the investigator will make sure that all data are recorded in the eCRFs. The investigator will allow the monitor access to the "source" data and essential documents and must provide support at all times to the monitor.

During the monitoring visit, the monitor will check with the investigator the progress of the trial and protocol compliance as assessed by the data recorded in the eCRFs. The investigator(s) must agree to permit the monitor to be present to observe the study procedure in one or more patients.

9.2 Source Documents

For each patient included in the study, a specific file (i.e., institution file) must exist with original data, on which is based the information recorded in the eCRF.

Source documents and eCRFs must not be exact copies of each other. As a general rule, medical information that is not specifically required by the study (e.g. patient's sex, prior medical history, prior medication, etc.) must be found in source medical documents (and in the eCRF). Information specifically required by the protocol and not required by routine clinical care may be recorded directly in the eCRF without appearing in source documents. In addition, source documents must mention that the patient has been included in an investigational study. Finally, there must be no data that are inconsistent between eCRF and source documents.

9.3 Inspection / Audits

Regulatory authorities or an auditor authorized by the sponsor may request access to all source documents, eCRF, and other trial documentation. Direct access to these documents must be guaranteed by the investigator who must provide support at all times for these activities. Patients will be generally informed about this opportunity during informed consent procedure.

10 ETHICAL AND LEGAL ASPECTS

10.1 Good clinical practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by Good Clinical Practice (GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

10.2 Patient information and informed consent

Before being admitted to the clinical trial, the patient must consent to participate after the nature, scope, and possible consequences of the clinical trial have been explained in a form understandable to him or her. The patient must give consent in writing. The signed Informed Consent Form will be filed by the investigator.

A copy of the signed informed consent document must be given to the patient. The documents must be in a language understandable to the patient and must specify who informed the patient.

The patients will be informed as soon as possible if new information may influence his/her decision to participate in the trial. The communication of this information should be documented.

10.3 Confidentiality

The data obtained in the course of the trial will be treated pursuant to the Federal Data Protection Law.

During the clinical trial, patients will be identified solely by date of birth, and an individual identification code (country number, site number, patient number). Trial findings stored on a computer will be stored in accordance with local data protection law and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation will be fulfilled in its entirety.

The patient consents in writing to release the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorized persons (inspectors, monitors, auditors). Authorized persons (clinical monitors, auditors, inspectors) may inspect the patient-related data collected during the trial ensuring the data protection law.

The investigator will maintain a patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

Patients who did not consent to circulate their pseudonymized data will not be included into the trial.

10.4 Responsibilities of investigator

The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the trial treatments, and their trial-related duties and functions.

The investigator should maintain a list of subinvestigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

10.5 Approval of trial protocol and amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent Ethics Committee (EC) as well as to the competent higher federal authority. A written favorable vote of the EC and an (implicit)

approval by the competent higher federal authority are a prerequisite for initiation of this clinical trial. The statement of EC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member. This documentation must also include a list of members of the EC present on the applicable EC meeting and a GCP compliance statement.

Before the first patient is enrolled in the trial, all ethical and legal requirements must be met. All planned substantial changes will be submitted to EC and the competent higher federal authority in writing as protocol amendments. They have to be approved by the EC and the competent higher federal authority.

The investigator and the CRO will keep a record of all communication with the EC and the regulatory authorities.

10.6 Continuous information to independent ethics committee

Persuant to GCP Ordinance, the EC and the competent higher federal authority will be informed of all suspected serious unexpected adverse reactions (SUSARs) and all AEs resulting in death or being live-threatening occurring during the trial. Both institutions will be informed in case the risk/ benefit assessment did change or any others new and significant hazards for patients' safety or welfare did occur. Furthermore, a report on all observed serious adverse events (SAEs) will be submitted once a year – Developmental Safety Update Report (DSUR).

The EC and the regulatory authorities must be informed of the end of the trial. They will be provided with a summary of trial results within one year after the end of clinical phase (LPO).

10.7 Notification to regulatory authorities

The local regulatory authorities responsible for each particular investigator will be informed before the beginning, during and at the end of the trial according to the applicable regulations. Each investigator is obliged to notify his/ her local regulatory authority. This responsibility has been delegated to the CRO.

10.8 Registration of the trial

Prior to the beginning of the clinical phase (FPI), the CRO will register the trial at Current Controlled Trials (https://www.clinicaltrialsregister.eu/index.html, http://www.controlled-trials.com or http://www.clinicaltrials.gov). Thus the trial will be given a unique ISRCTN, which is a prerequisite for a publication in a peer-reviewed medical journal.

10.9 Insurance

For patients enrolled in this clinical trial, the sponsor will contract a patient insurance.

Any impairment of health which might occur in consequence of trial participation must be notified to the insurance company. The patient is responsible for notification. The insured person will agree with all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.

During the conduct of the trial, the patient must not undergo other clinical treatment except for cases of emergency. The patient is bound to inform the investigator immediately about any adverse events and additionally drugs taken. The terms and conditions of the insurance should be delivered to the patient.

The insurance company has to be informed about all amendments that could affect the patient's safety.

11 STATISTICAL METHODS

11.1 Methods of Statistical Analysis

Statistical methods will be described in detail in the Statistical Analysis Plan (SAP).

The trial objectives will be evaluated by statistical hypothesis testing, summary tables and figures and by data listings.

All analyses will be performed using SAS® Version 9.2 or later and SAS JMP Version

10 or later.

11.2 Analysis Sets

11.2.1 Progressors and Non-Progressors

There will be two patient groups, both receiving the same treatment medication, which will be analysed separately. Depending on whether the disease is rapidly progressing during the run-in phase, patients are either assigned to the progressor (Group A) or the non-progressor group (Group B) at the time of enrolment. The main efficacy analysis will solely be based on the progressor group while the safety analysis will be based on the pooled data from progressors and non-progressors. Additional analyses will be performed on progressors and non-progressors individually and on the pooled set. These analyses are considered as supportive.

Safety Set The safety set consists of all enrolled patients for whom infusion of study medication had been started. All safety analyses will be performed on the safety set.

11.2.2 Full Analysis Sets (FAS)

The FAS sets for progressors (Group A) and non-progressors (Group B) consist of all patients in the corresponding group for whom infusion of study medication had been started, and for whom at least one post baseline measurement of the total wound area will be available. Even though it is expected, that there will be a significant number of drop-outs, most of these drop-outs will likely occur at a later stage of the treatment, i.e. after V1 (see 11.2.4). The FAS datasets as defined here should therefore include almost all enrolled patients.

All efficacy analyses will be performed primarily on the FAS subset of the progressors group, i.e. Group A.

11.2.3 Per Protocol Set (PPS)

The PPS sets consist of all randomized patients in the corresponding group included in the FAS, but will exclude the following:

- patients violating major inclusion/exclusion criteria related to efficacy;
- patients deviating from the protocol in an extent that causes bias for efficacy evaluation (e.g. no 24-week efficacy data available);
- patients with severe disease status which may be switched to STS treatment earlier than 2 weeks.

The final exclusion of patients from the PPS will be done at the blind review meeting on an individual patient basis.

All relevant efficacy analyses will also be conducted on the PPS. These analyses are considered as supportive for the analyses performed on FAS.

11.2.4 Missing value treatment

There is a variety of possible reasons for missing values, mostly due to the very aggressive nature of the disease, the generally very bad health state of the patients and their low life expectancy. Drop-outs due to severe treatment side effects are by contrast rather unlikely, partly because STS is generally well tolerated, partly because dose reduction is a possible alternative to a complete stop of treatment.

Nevertheless, the possibly incomplete list of drop-out reasons includes nausea, extreme pain, infections, the complete stop of treatment, transplantation, or patient's death. Apart from nausea, all other reasons are likely not treatment related. It is also expected, that drop-outs will occur with an approximately constant rate. Therefore, at least V1 data should be available for most patients.

Due to the longitudinal assessment schedule of the efficacy parameters, the use of a pattern mixture model for missing value treatment will likely provide better results than the use of the Last Observation Carried Forward (LOCF) method or other simple approaches. Details will be given in the SAP.

11.3 Baseline

Baseline measurements of the relevant efficacy and safety variables will be taken after enrolment of the patient for starting of STS treatment. Change from baseline will be calculated

as the difference in post-baseline versus baseline values. Selected pre-baseline measurements (from start of the run-in phase) will be analyzed exploratively.

11.4 Descriptive Statistics

Categorical data will be summarized by means of absolute and relative frequencies (counts and percentages). Continuous data will be summarized by means of the following summary statistics: number of observations, arithmetic mean, standard deviation, minimum, median, maximum and quartiles.

Where appropriate, data will be visualized by means of box-whisker plots, arithmetic mean courses over time or Kaplan-Meier Plots for censored data.

11.5 Analysis of Efficacy

The main statistical analysis of the primary efficacy variable will be performed on the FAS of the progressors group (Group A) using the missing value handling approach as described in 11.2.4 Additional analyses on the PPS will be considered as supportive. If no efficacy data has been recorded before death and cause of death will be clearly unrelated to the treatment, the patient will be removed from the analysis.

11.5.1 Primary Efficacy Analysis

Change in total wound area until between baseline and V4 (24 weeks after start of medication) will be analyzed as the primary efficacy variable. At V0 and V4 photographs of all wounds are taken according to the description in section 5.2. The size in square centimeters of each individual wound will be assessed by two independent and blinded dermatologists using appropriate image analysis software and the means of both assessments will be calculated for each time point. The dermatologists will neither know at what time point images were taken nor will they know that two sets of images show the same patient at a different time point.

The mean area of each wound of a given patient at a given time point will then be summed up over all wounds and used to calculate the percent change in wound size.

As stated before, calciphylaxis is a highly progressive disease with rapidly deteriorating skin lesions. Without treatment or treated with standard medication, a clear worsening of lesions between V0 and V4 would take place. On the other hand, based on literature data and

information from physicians, a decrease in wound size of 20% or more under STS treatment can clearly be considered as clinically relevant, because wound size is correlated with the detrimental symptoms of calciphylaxis and such a decrease in wound size would be a notable improvement for patient condition.

The change in total wound area will be analyzed using a One-sample Wilcoxon Signed Rank test. The sample median together with the corresponding confidence interval will also be given.

11.5.2 Secondary Efficacy Analysis

Pain reduction and the consumption of pain medication after 4, 8, 16, 24, 36 and 48 weeks compared to baseline will both be treated as continuous variables and independently analyzed using One-sample Wilcoxon Signed Rank Tests with a pattern mixture model approach for missing data.

Untreated pain level and/or the consumption of pain medication will significantly increase over time as the disease progresses. Any significant decrease in either parameter is a strong signal for a positive treatment effect. Even though there is supposedly a strong negative correlation between the two parameters, they will be analyzed individually at an alpha level of 0.025 one sided. Additionally, for every patient, pain level and medication consumption will be plotted as a time course covering all visits from VR to V6.

Bone mineral density (BMD) will be tabulated and analyzed descriptively.

Patient survival will be tabulated descriptively and visualized using a Kaplan Meier plot. Additionally, the overall survival after start of STS treatment and the one-year survival rate will be explicitely stated.

The assessment of total wound area, skin lesions using the revPWAT score and the clinical global impression using the CGI-S scale and CGI-I score will be tabulated descriptively and plotted as a time-course using box-whisker plots.

Patients with total remission of the wound area will be listed with the corresponding time after beginning of STS treatment. The fraction of patients with total wound remission, and for these patients, descriptive statistics about time to remission will also be provided.

Accordingly, the use of wound debridement and change in the eligibility of patients for kidney transplantation will also be analyzed

11.6 Analysis of Safety

Safety and tolerability will be assessed in terms of AEs and vital signs, and laboratory parameters will be determined using the safety analysis set. The number of AEs, which are reported in addition to the symptom complexes considered as AEs from the underlying disease, and the number and percentage of patients reporting at least one AE will be summarized by system organ class (SOC), preferred term (PT), treatment group and overall. When counting patients, an AE reported more than once will be counted only once but with its highest degree of severity. An AE will be considered treatment-emergent (TEAE), if it occurs for the first time, or worsens in terms of seriousness or severity. Summaries of treatment-emergent serious AEs, AEs leading to withdrawal, AESIs and AEs by severity and relationship to study medication will be presented.

No statistical hypothesis testing is intended on safety and tolerability data.

11.7 Laboratory Parameters

All laboratory data will be analyzed using descriptive statistics. Additionally, the number of patients with laboratory values below, within and above normal range will be determined for each parameter and time point.

11.8 Sample Size Estimation

11.8.1 Calculation procedure

There is no straightforward sample size calculation possible for this study. Firstly, neither reliable estimates for the effect size nor for the variability of the treatment effect are known, secondly, a relatively high drop-out rate is expected based on data from the literature. Sample size is therefore chosen both based on rough estimates of effect size and variability and on feasibility considerations, the latter mainly effected by the low incidence of calciphylaxis. Another issue which needs to be considered is the fact, that only patients with progressing calciphylaxis will be assigned to the efficacy analysis group (Group A). However it is expected, that the number of non-progressors will be very small.

Sample size calculation for the confirmatory efficacy parameter is performed using version 3.17 of the G*Power application. Power is set to 80%, maximum alpha error to 0.05 two sided corresponding to 0.025 one-sided.

11.8.2 Reduction in total wound area

Percent reduction in total wound area will be analyzed as the primary efficacy variable. A median reduction of at least 50%, significantly higher than the 20% reduction which are already considered as clinically relevant are expected for this parameter. The standard deviation for this parameter should be no higher than approximately 100%: This results in a standardized effect size (Cohen's d) of about 0.6 and a sample size of about 25 patients. This number needs to be increased for two reasons. Firstly, only patients which show progressing disease status during the run-in phase will be included in the efficacy analysis group and secondly, there is a relatively high risk of drop-outs. In a calciphylaxis study (clinicaltrials.gov identifier: NCT00568399), only 60% of the study participants actually completed the study. For the current study, patients will be analyzed if at least one post recruitment score will be available. This should be the case for the majority of the patients. Nevertheless to account for the reasons mentioned above, the sample size will be increased by 50% and a total sample size of 40 patients will be used.

This number should provide good estimates with small enough confidence intervals for both the primary and possibly also for one or more of the secondary efficacy parameters.

12 AGREEMENTS

12.1 Financing of the Clincial Trial

The clinical trial will be financed by Dr. F. Köhler Chemie GmbH.

12.2 Financial Disclosure

Before the start of the trial, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the sponsors, in the investigational product or any commercial organisation being involved in the clinical trial. The investigator has also to confirm that he/she has not entered into any financial arrangement, whereby the value of compensation paid could affect the outcome of the clinical trial.

The investigator agrees to update this information in case of significant changes.

12.3 Reports

The *CRO* will prepare the integrated report according to ICH E3, in agreement with the sponsor.

12.4 Publication

The results will be published, preferably in a Nephrological or General Medicine Journal. All information concerning the trial is confidential before publication. Paying due regard to statutory rights and duties of a university, the investigators shall be entitled to publish, in consultation with the sponsor and after completion of the research work, the scientific findings for scientific purpose. A manuscript of the intended publication must be submitted to the sponsor (Dr. F. Köhler Chemie GmbH) for scrutiny at the latest 60 days prior to publication. Proposals for changes and modifications submitted by the sponsor ought to be taken into consideration, unless said proposals interfere with the scientific nature or the neutrality of the publication. A publication of the results in an international peer-reviewed journal is planned at the end of study.

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EudraCT-Nr. 2014-002128-28

Declaration of Consent

The clinical trial STS-CSM-1/13 will be conducted in accordance with the EU recommendations on "Good Clinical Practice (GCP)". It is certified that the trial plan, the documentation file and the appendices all contain the items of information and decisions necessary for the conduct of the study, and the study will be carried out and documented in accordance with this trial plan and that the legislative provisions and the agreements described will be adhered to.

Signature list:

Name	Function	Date	Signature
Dr. Roman Petrov Dr. F. Köhler Chemie GmbH	Sponsor	23.06.2015	
Dr. Gerhard Vogt PharmaLex GmbH	Biostatistician		

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Dr. Roman Petrov Dr. F. Köhler Chemie GmbH	Sponsor		
Dr. Gerhard Vogt PharmaLex GmbH	Biostatistician	23. Jun 2015	G. Vf

16.1.2 Sample case report form

The following documents are included in this section:

- eCRF Hardcopy, Version, FINAL 5.0, dated 22-Jan-2018

Screening/Start of run-in phase

Demographic information [CRF-page 1/17]	
Date of written informed consent (1/5)	__/__/20__ [day/month/year]
Patient ID (2/5)	__-__-___ (country-site-patient)
Patient year of birth (3/5)	19__ [year] Age (at date of informed consent): ___ years
Gender (4/5)	[[male female]]
Race of patient (5/5)	[[white black asiatic other]] if other - please specify: _____ _____ _____

Inclusion/exclusion criteria [CRF-page 2/17]	
Inclusion criteria	
Patient ≥ 18 years (1/11)	[[yes no]]
Male or female HD patients with a diagnosis of calciphylaxis (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching) (2/11)	[[yes no]]
Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study (3/11)	[[yes no]]
Exclusion criteria	
Sodium metabisulfite hypersensitivity, among others the history of bronchial asthma due to known sodium metabisulfite hypersensitivity (4/11)	[[yes no]]
Pregnant or lactating patients. As pregnancy is an extremely rare event in HD patients, a pregnancy test will only be performed in ambiguous cases. (5/11)	[[yes no]]
Females who are pregnant (positive pregnancy test at screening or during study phase) or lactating. If having reproductive potential are considered potentially ineligible with respect to use highly effective methods of birth control throughout the study. (6/11)	[[yes no]]
Patients who have participated in any other investigational studies within 30 days previous to enrollment (7/11)	[[yes no]]
History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment (8/11)	[[yes no]]
Good response to conventional treatment (9/11)	[[yes no]]
Life expectancy less than 4 months in the judgement of the investigator (10/11)	[[yes no]]
Comments (11/11)	

Clinical examination [CRF-page 3/17]	
Vital signs	
Date of assessment (1/24)	__/__/20__ [day/month/year]
Body height (2/24)	___ cm
Body weight (3/24)	___._ kg
Blood pressure (measured after patient has rested for 5 minutes) (4/24)	___ mmHg / ___ mmHg [systolic/diastolic]
Heart rate (measured after patient has rested for 5 minutes) (5/24)	___ b/min
BMI (calculated) (6/24)	___._ kg/m²
12-lead ECG	
ECG findings (7/24)	Date: __/__/20__ [day/month/year] Result: [[normal abnormal, not clinically relevant abnormal, clinically relevant]] if abnormal and clinically relevant - please specify: _____ _____ _____
Physical examination	
Were physical examinations performed (8/24)	[[yes no]] if yes - date: __/__/20__ [day/month/year]
Head (9/24)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Eye, ear, nose, throat (10/24)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Cardiovascular (11/24)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Dermatological (12/24)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Musculosceletal (13/24)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Respiratory (14/24)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Gastrointestinal (15/24)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Neurological (16/24)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Other (17/24)	[[normal abnormal not done]] if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Calciphylaxis diagnosis	
Calciphylaxis diagnosed according to typical signs and symptoms (18/24)	[[yes no]] if yes - please check all that apply: [ ] Severe pain [ ] Livedo [ ] Violaceous plaques [ ] Ulcerations [ ] Necroses if ulcerations and/or necroses - have other causes been excluded: [[yes no]]
Tobacco use	
Tobacco use (19/24)	[[Smoker Non-smoker]]
Checklist	
Does the patient have any relevant medical history or concomitant diseases (20/24)	[[yes no]]
Does the patient receive any concomitant medication (including pain medication) (21/24)	[[yes no]]
Any concomitant procedures/measures performed (22/24)	[[yes no]]
Has sample for biobanking been taken (23/24)	[[yes no]] if yes - date: __/__/20__ [day/month/year]
Comments (24/24)	_____ _____ _____

Hematology and venous blood gas analysis [CRF-page 4/17]	
Hematology	
Date of sample (1/12)	__/__/20__ [day/month/year]
Patient's age at sampling date (2/12)	[ ] same as at informed consent (___ years) or ___ years
Hemoglobin (3/12)	_____._____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
White blood cells (4/12)	_____._____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min [ ] not available
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____._____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Partial pressure of oxygen venous (8/12)	_____._____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Oxygen saturation (9/12)	_____._____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Bicarbonate (10/12)	_____._____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	_____ _____ _____

Clinical chemistry [CRF-page 5/17]	
Clinical Chemistry	
Date of sample (1/25)	__/__/20__ [day/month/year]
Patient's age at sampling date (2/25)	[ ] same as at informed consent (___ years) or ___ years
IPTH (3/25)	_____._____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Calcium (4/25)	_____._____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Phosphate (5/25)	_____._____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Alk. phosphatase (6/25)	_____._____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
pH serum (7/25)	_____._____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
C-reactive protein (CRP) (8/25)	_____._____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Creatinine (9/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Albumin (10/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Sodium (11/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Potassium (12/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Chloride (13/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Magnesium (14/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

GOT (AST) (15/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
GPT (ALT) (16/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Gamma-GT (17/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Amylase (18/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Lipase (19/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Urea (20/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Uric acid (21/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
1,25-Dihydroxy-Vitamine D (22/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
25-Hydroxy-Vitamin D (23/25)	_____.____ _____ if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____

Wound, pain and other assessments [CRF-page 6/17]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/4)	[[yes no]]
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/4)	[[yes no]] if yes - degree of pain: ___ mm
Pregnancy test	
Pregnancy test (3/4)	[[positive negative not done not applicable (e.g. menopause, hysterectomy)]] Date:__/__/20__ [day/month/year]
Comments (4/4)	_____ _____ _____

End of run-in phase

Inclusion/exclusion criteria [CRF-page 7/17]	
Inclusion criteria	
Patient ≥ 18 years (1/11)	[[yes no]]
Male or female HD patients with a diagnosis of calciphylaxis. (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching). (2/11)	[[yes no]]
Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study (3/11)	[[yes no]]
Exclusion criteria	
Sodium metabisulfite hypersensitivity, among others the history of bronchial asthma due to known sodium metabisulfite hypersensitivity (4/11)	[[yes no]]
Pregnant or lactating patients. As pregnancy is an extremely rare event in HD patients, a pregnancy test will only be performed in ambiguous cases. (5/11)	[[yes no]]
Females who are pregnant (positive pregnancy test at screening or during study phase) or lactating. If having reproductive potential are considered potentially ineligible with respect to use highly effective methods of birth control throughout the study. (6/11)	[[yes no]]
Patients who have participated in any other investigational studies within 30 days previous to enrollment (7/11)	[[yes no]]
History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment (8/11)	[[yes no]]
Good response to conventional treatment (9/11)	[[yes no]]
Life expectancy less than 4 months in the judgement of the investigator (10/11)	[[yes no]]
Comments (11/11)	

Completion of run-in-phase [CRF-page 8/17]	
Biopsy report of consisting wound available (1/7)	[[yes no]] if yes: please check all that apply: [ ] none [ ] diagnosis of calciphylaxis confirmed [ ] other causes for necroses and ulcerations excluded
Has a skin biopsy been taken (2/7)	[[yes no]] if yes, date:__/__/20__ [day/month/year] if yes - calciphylaxis diagnosis confirmed by analysis: [[yes no]]
Has the patient agreed to participate in the clinical trial and to undergo STS treatment (3/7)	[[yes no]]
Disease status under BSC (4/7)	[[rapidly progressive disease less progressive disease initially stable disease]]
Have all screening/baseline assessments been performed and is patient considered eligible for treatment start (5/7)	[[yes no]] if no - please check all that apply: [ ] patient did not meet all in-/exclusion criteria [ ] withdrawal of informed consent by the patient [ ] discretion of the investigator [ ] calciphylaxis diagnosis not confirmed [ ] other reason if other reason - please specify: _____ _____ _____
Has all patient data been entered as far as possible and checked, all data can be set read-only (6/7)	[[yes no]]
Comments (7/7)	_____ _____ _____

Visits

Visits [CRF-page 9/17] - Table

Visit 0	
Start of visit [Instance-no: 1, page 1/5]	
Actual date of visit (1/6)	__/__/20__ [day/month/year] [ ] not done
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (2/6)	[[yes no]]
Any new concomitant procedures/measures or changes in concomitant procedures/measures (3/6)	[[yes no]]
Any new adverse events or changes in adverse events (4/6)	[[yes no]]
Soft tissue radiographs	
Have soft tissue radiographs been taken (optional) (5/6)	[[yes no]] if yes, date: __/__/20__ [day/month/year]
Comments (6/6)	

Clinical examination [Instance-no: 1, page 2/5]	
Vital signs	
Date of assessment (1/17)	__/__/20__ [day/month/year]
Body weight (2/17)	___._ kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	___ mmHg / ___ mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	___ b/min [ ] not done
BMI (calculated) (5/17)	___._ kg/m²
Physical examination	
Were physical examinations performed (6/17)	[[yes no]] if yes - date: __/__/20__ [day/month/year]
Head (7/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Eye, ear, nose, throat (8/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Cardiovascular (9/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Dermatological (10/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Musculosceletal (11/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Respiratory (12/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Gastrointestinal (13/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Neurological (14/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Other (15/17)	[[normal abnormal not done]] if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Biobanking	
Has sample for biobanking been taken (16/17)	[[yes no]] if yes - date: __/__/20__ [day/month/year]
Comments (17/17)	_____ _____ _____

Hematology and venous blood gas analysis [Instance-no: 1, page 3/5]	
Hematology	
Date of sample (1/12)	__/__/20__ [day/month/year]
Patient's age at sampling date (2/12)	[ ] same as at informed consent (___ years) or ___ years
Hemoglobin (3/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
White blood cells (4/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min [ ] not available
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Partial pressure of oxygen venous (8/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Oxygen saturation (9/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Bicarbonate (10/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	_____ _____ _____

Clinical chemistry [Instance-no: 1, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	__/__/20__ [day/month/year]
Patient's age at sampling date (2/25)	[ ] same as at informed consent (___ years) or ___ years
IPTH (3/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Calcium (4/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Phosphate (5/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Alk. phosphatase (6/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
pH serum (7/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
C-reactive protein (CRP) (8/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Creatinine (9/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Albumin (10/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Sodium (11/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Potassium (12/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Chloride (13/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Magnesium (14/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

GOT (AST) (15/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
GPT (ALT) (16/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Gamma-GT (17/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Amylase (18/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Lipase (19/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Urea (20/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Uric acid (21/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
1,25-Dihydroxy-Vitamine D (22/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
25-Hydroxy-Vitamin D (23/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____

Wound, pain and other assessments [Instance-no: 1, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	[[yes no]]
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	[[yes no]] if yes - degree of pain: ___ mm
Pregnancy test	
Pregnancy test (3/6)	[[positive negative not done not applicable (e.g. menopause, hysterectomy)]] Date:__/__/20__ [day/month/year]
Bone Mineral Density	
Has bone mineral density been assessed (4/6)	[[yes no]] if yes: method:[[DEXA scan CT]] t-score:__.__ z-score:__.__
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (5/6)	[[yes no]] if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: [[normal, not at all ill borderline mentally ill mildly ill moderately ill markedly ill severely ill extremely ill]]
Comments (6/6)	_____ _____ _____

Visit 1	
Start of visit [Instance-no: 2, page 1/3]	
Planned date of visit (1/7)	__/__/____ [day/month/year]
Actual date of visit (2/7)	__/__/20__ [day/month/year] [ ] not done if deviation from planned date - please provide reason: _____ _____ _____
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	[[yes no]]
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	[[yes no]]
Any new adverse events or changes in adverse events (5/7)	[[yes no]]
Any new lesions under STS treatment (6/7)	[[yes no]]
Comments (7/7)	_____ _____ _____

Clinical examination [Instance-no: 2, page 2/3]	
Vital signs	
Date of assessment (1/16)	__/__/20__ [day/month/year]
Body weight (2/16)	___._ kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/16)	___ mmHg / ___ mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/16)	___ b/min [ ] not done
BMI (calculated) (5/16)	___._ kg/m²
Physical examination	
Were physical examinations performed (6/16)	[[yes no]] if yes - date: __/__/20__ [day/month/year]
Head (7/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Eye, ear, nose, throat (8/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Cardiovascular (9/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Dermatological (10/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Musculosceletal (11/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Respiratory (12/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Gastrointestinal (13/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Neurological (14/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Other (15/16)	[[normal abnormal not done]] if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Comments (16/16)	_____ _____ _____

Wound, pain and other assessments [Instance-no: 2, page 3/3]	
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (1/5)	[[yes no]] if yes - degree of pain: ___ mm
Pregnancy test	
Pregnancy test (2/5)	[[positive negative not done not applicable (e.g. menopause, hysterectomy)]] Date:__/__/20__ [day/month/year]
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (3/5)	[[yes no]] if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: [[normal, not at all ill borderline mentally ill mildly ill moderately ill markedly ill severely ill extremely ill]]
Was the clinical global impression improvement assessed using the CGI-I-score (4/5)	[[yes no]] if yes: Compared to the patient’s condition at the baseline visit (V0), this patient’s condition is: [[very much improved since the initiation of treatment much improved minimally improved no change from baseline (the initiation of treatment) minimally worse much worse very much worse since the initiation of treatment]]
Comments (5/5)	_____ _____ _____

Visit 2	
Start of visit [Instance-no: 3, page 1/5]	
Planned date of visit (1/7)	__/__/____ [day/month/year]
Actual date of visit (2/7)	__/__/20__ [day/month/year] [ ] not done if deviation from planned date - please provide reason: _____ _____ _____
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	[[yes no]]
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	[[yes no]]
Any new adverse events or changes in adverse events (5/7)	[[yes no]]
Any new lesions under STS treatment (6/7)	[[yes no]]
Comments (7/7)	_____ _____ _____

Clinical examination [Instance-no: 3, page 2/5]	
Vital signs	
Date of assessment (1/17)	__/__/20__ [day/month/year]
Body weight (2/17)	___._ kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	___ mmHg / ___ mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	___ b/min [ ] not done
BMI (calculated) (5/17)	___._ kg/m²
Physical examination	
Were physical examinations performed (6/17)	[[yes no]] if yes - date: __/__/20__ [day/month/year]
Head (7/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Eye, ear, nose, throat (8/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Cardiovascular (9/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Dermatological (10/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Musculosceletal (11/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Respiratory (12/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Gastrointestinal (13/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Neurological (14/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Other (15/17)	[[normal abnormal not done]] if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Biobanking	
Has sample for biobanking been taken (16/17)	[[yes no]] if yes - date: __/__/20__ [day/month/year]
Comments (17/17)	_____ _____ _____

Hematology and venous blood gas analysis [Instance-no: 3, page 3/5]	
Hematology	
Date of sample (1/12)	__/__/20__ [day/month/year]
Patient's age at sampling date (2/12)	[ ] same as at informed consent (___ years) or ___ years
Hemoglobin (3/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
White blood cells (4/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min [ ] not available
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Partial pressure of oxygen venous (8/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Oxygen saturation (9/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Bicarbonate (10/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	_____ _____ _____

Clinical chemistry [Instance-no: 3, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	__/__/20__ [day/month/year]
Patient's age at sampling date (2/25)	[ ] same as at informed consent (___ years) or ___ years
IPTH (3/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Calcium (4/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Phosphate (5/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Alk. phosphatase (6/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
pH serum (7/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
C-reactive protein (CRP) (8/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Creatinine (9/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Albumin (10/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Sodium (11/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Potassium (12/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Chloride (13/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Magnesium (14/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

GOT (AST) (15/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
GPT (ALT) (16/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Gamma-GT (17/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Amylase (18/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Lipase (19/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Urea (20/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Uric acid (21/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
1,25-Dihydroxy-Vitamine D (22/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
25-Hydroxy-Vitamin D (23/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____

Wound, pain and other assessments [Instance-no: 3, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	[[yes no]]
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	[[yes no]] if yes - degree of pain: ___ mm
Pregnancy test	
Pregnancy test (3/6)	[[positive negative not done not applicable (e.g. menopause, hysterectomy)]] Date:__/__/20__ [day/month/year]
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (4/6)	[[yes no]] if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: [[normal, not at all ill borderline mentally ill mildly ill moderately ill markedly ill severely ill extremely ill]]
Was the clinical global impression improvement assessed using the CGI-I-score (5/6)	[[yes no]] if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: [[very much improved since the initiation of treatment much improved minimally improved no change from baseline (the initiation of treatment) minimally worse much worse very much worse since the initiation of treatment]]
Comments (6/6)	_____ _____ _____

Visit 3	
Start of visit [Instance-no: 4, page 1/5]	
Planned date of visit (1/7)	__/__/____ [day/month/year]
Actual date of visit (2/7)	__/__/20__ [day/month/year] [ ] not done if deviation from planned date - please provide reason: _____ _____ _____
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	[[yes no]]
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	[[yes no]]
Any new adverse events or changes in adverse events (5/7)	[[yes no]]
Any new lesions under STS treatment (6/7)	[[yes no]]
Comments (7/7)	_____ _____ _____

Clinical examination [Instance-no: 4, page 2/5]	
Vital signs	
Date of assessment (1/17)	__/__/20__ [day/month/year]
Body weight (2/17)	___._ kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	___ mmHg / ___ mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	___ b/min [ ] not done
BMI (calculated) (5/17)	___._ kg/m²
Physical examination	
Were physical examinations performed (6/17)	[[yes no]] if yes - date: __/__/20__ [day/month/year]
Head (7/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Eye, ear, nose, throat (8/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Cardiovascular (9/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Dermatological (10/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Musculosceletal (11/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Respiratory (12/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Gastrointestinal (13/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Neurological (14/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Other (15/17)	[[normal abnormal not done]] if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Biobanking	
Has sample for biobanking been taken (16/17)	[[yes no]] if yes - date: __/__/20__ [day/month/year]
Comments (17/17)	_____ _____ _____

Hematology and venous blood gas analysis [Instance-no: 4, page 3/5]	
Hematology	
Date of sample (1/12)	__/__/20__ [day/month/year]
Patient's age at sampling date (2/12)	[ ] same as at informed consent (___ years) or ___ years
Hemoglobin (3/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
White blood cells (4/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min [ ] not available
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Partial pressure of oxygen venous (8/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Oxygen saturation (9/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Bicarbonate (10/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	_____ _____ _____

Clinical chemistry [Instance-no: 4, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	__/__/20__ [day/month/year]
Patient's age at sampling date (2/25)	[ ] same as at informed consent (___ years) or ___ years
IPTH (3/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Calcium (4/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Phosphate (5/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Alk. phosphatase (6/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
pH serum (7/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
C-reactive protein (CRP) (8/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Creatinine (9/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Albumin (10/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Sodium (11/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Potassium (12/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Chloride (13/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Magnesium (14/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

GOT (AST) (15/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
GPT (ALT) (16/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Gamma-GT (17/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Amylase (18/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Lipase (19/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Urea (20/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Uric acid (21/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
1,25-Dihydroxy-Vitamine D (22/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
25-Hydroxy-Vitamin D (23/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____

Wound, pain and other assessments [Instance-no: 4, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	[[yes no]]
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	[[yes no]] if yes - degree of pain: ___ mm
Pregnancy test	
Pregnancy test (3/6)	[[positive negative not done not applicable (e.g. menopause, hysterectomy)]] Date:__/__/20__ [day/month/year]
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (4/6)	[[yes no]] if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: [[normal, not at all ill borderline mentally ill mildly ill moderately ill markedly ill severely ill extremely ill]]
Was the clinical global impression improvement assessed using the CGI-I-score (5/6)	[[yes no]] if yes: Compared to the patient’s condition at the baseline visit (V0), this patient’s condition is: [[very much improved since the initiation of treatment much improved minimally improved no change from baseline (the initiation of treatment) minimally worse much worse very much worse since the initiation of treatment]]
Comments (6/6)	_____ _____ _____

Visit 4	
Start of visit [Instance-no: 5, page 1/5]	
Planned date of visit (1/7)	__/__/____ [day/month/year]
Actual date of visit (2/7)	__/__/20__ [day/month/year] [ ] not done if deviation from planned date - please provide reason: _____ _____ _____
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	[[yes no]]
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	[[yes no]]
Any new adverse events or changes in adverse events (5/7)	[[yes no]]
Any new lesions under STS treatment (6/7)	[[yes no]]
Comments (7/7)	_____ _____ _____

Clinical examination [Instance-no: 5, page 2/5]	
Vital signs	
Date of assessment (1/17)	__/__/20__ [day/month/year]
Body weight (2/17)	___._ kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	___ mmHg / ___ mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	___ b/min [ ] not done
BMI (calculated) (5/17)	___._ kg/m²
Physical examination	
Were physical examinations performed (6/17)	[[yes no]] if yes - date: __/__/20__ [day/month/year]
Head (7/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Eye, ear, nose, throat (8/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Cardiovascular (9/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Dermatological (10/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Musculosceletal (11/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Respiratory (12/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Gastrointestinal (13/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Neurological (14/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Other (15/17)	[[normal abnormal not done]] if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Biobanking	
Has sample for biobanking been taken (16/17)	[[yes no]] if yes - date: __/__/20__ [day/month/year]
Comments (17/17)	_____ _____ _____

Hematology and venous blood gas analysis [Instance-no: 5, page 3/5]	
Hematology	
Date of sample (1/12)	__/__/20__ [day/month/year]
Patient's age at sampling date (2/12)	[ ] same as at informed consent (___ years) or ___ years
Hemoglobin (3/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
White blood cells (4/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min [ ] not available
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Partial pressure of oxygen venous (8/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Oxygen saturation (9/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Bicarbonate (10/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	_____ _____ _____

Clinical chemistry [Instance-no: 5, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	__/__/20__ [day/month/year]
Patient's age at sampling date (2/25)	[ ] same as at informed consent (___ years) or ___ years
IPTH (3/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Calcium (4/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Phosphate (5/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Alk. phosphatase (6/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
pH serum (7/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
C-reactive protein (CRP) (8/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Creatinine (9/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Albumin (10/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Sodium (11/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Potassium (12/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Chloride (13/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Magnesium (14/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

GOT (AST) (15/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
GPT (ALT) (16/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Gamma-GT (17/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Amylase (18/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Lipase (19/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Urea (20/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Uric acid (21/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
1,25-Dihydroxy-Vitamine D (22/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
25-Hydroxy-Vitamin D (23/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____

Wound, pain and other assessments [Instance-no: 5, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	[[yes no]]
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	[[yes no]] if yes - degree of pain: ___ mm
Pregnancy test	
Pregnancy test (3/6)	[[positive negative not done not applicable (e.g. menopause, hysterectomy)]] Date:__/__/20__ [day/month/year]
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (4/6)	[[yes no]] if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: [[normal, not at all ill borderline mentally ill mildly ill moderately ill markedly ill severely ill extremely ill]]
Was the clinical global impression improvement assessed using the CGI-I-score (5/6)	[[yes no]] if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: [[very much improved since the initiation of treatment much improved minimally improved no change from baseline (the initiation of treatment) minimally worse much worse very much worse since the initiation of treatment]]
Comments (6/6)	_____ _____ _____

Visit 5	
Start of visit [Instance-no: 6, page 1/3]	
Planned date of visit (1/7)	__/__/____ [day/month/year]
Actual date of visit (2/7)	__/__/20__ [day/month/year] [ ] not done if deviation from planned date - please provide reason: _____ _____ _____
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	[[yes no]]
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	[[yes no]]
Any new adverse events or changes in adverse events (5/7)	[[yes no]]
Any new lesions under STS treatment (6/7)	[[yes no]]
Comments (7/7)	_____ _____ _____

Clinical examination [Instance-no: 6, page 2/3]	
Vital signs	
Date of assessment (1/16)	__/__/20__ [day/month/year]
Body weight (2/16)	___._ kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/16)	___ mmHg / ___ mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/16)	___ b/min [ ] not done
BMI (calculated) (5/16)	___._ kg/m²
Physical examination	
Were physical examinations performed (6/16)	[[yes no]] if yes - date: __/__/20__ [day/month/year]
Head (7/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Eye, ear, nose, throat (8/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Cardiovascular (9/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Dermatological (10/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Musculosceletal (11/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Respiratory (12/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Gastrointestinal (13/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Neurological (14/16)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Other (15/16)	[[normal abnormal not done]] if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Comments (16/16)	_____ _____ _____

Wound, pain and other assessments [Instance-no: 6, page 3/3]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	[[yes no]]
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	[[yes no]] if yes - degree of pain: ___ mm
Pregnancy test	
Pregnancy test (3/6)	[[positive negative not done not applicable (e.g. menopause, hysterectomy)]] Date:__/__/20__ [day/month/year]
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (4/6)	[[yes no]] if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: [[normal, not at all ill borderline mentally ill mildly ill moderately ill markedly ill severely ill extremely ill]]
Was the clinical global impression improvement assessed using the CGI-I-score (5/6)	[[yes no]] if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: [[very much improved since the initiation of treatment much improved minimally improved no change from baseline (the initiation of treatment) minimally worse much worse very much worse since the initiation of treatment]]
Comments (6/6)	_____ _____ _____

Visit 6	
Start of visit [Instance-no: 7, page 1/5]	
Planned date of visit (1/7)	__/__/____ [day/month/year]
Actual date of visit (2/7)	__/__/20__ [day/month/year] [ ] not done if deviation from planned date - please provide reason: _____ _____ _____
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	[[yes no]]
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	[[yes no]]
Any new adverse events or changes in adverse events (5/7)	[[yes no]]
Any new lesions under STS treatment (6/7)	[[yes no]]
Comments (7/7)	_____ _____ _____

Clinical examination [Instance-no: 7, page 2/5]	
Vital signs	
Date of assessment (1/17)	__/__/20__ [day/month/year]
Body weight (2/17)	___._ kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	___ mmHg / ___ mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	___ b/min [ ] not done
BMI (calculated) (5/17)	___._ kg/m²
Physical examination	
Were physical examinations performed (6/17)	[[yes no]] if yes - date: __/__/20__ [day/month/year]
Head (7/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Eye, ear, nose, throat (8/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Cardiovascular (9/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Dermatological (10/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Musculosceletal (11/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Respiratory (12/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Gastrointestinal (13/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Neurological (14/17)	[[normal abnormal not done]] if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]

Other (15/17)	[[normal abnormal not done]] if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: [[yes no]]
Biobanking	
Has sample for biobanking been taken (16/17)	[[yes no]] if yes - date: __/__/20__ [day/month/year]
Comments (17/17)	_____ _____ _____

Hematology and venous blood gas analysis [Instance-no: 7, page 3/5]	
Hematology	
Date of sample (1/12)	__/__/20__ [day/month/year]
Patient's age at sampling date (2/12)	[ ] same as at informed consent (___ years) or ___ years
Hemoglobin (3/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
White blood cells (4/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min [ ] not available
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Partial pressure of oxygen venous (8/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Oxygen saturation (9/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Bicarbonate (10/12)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	_____ _____ _____

Clinical chemistry [Instance-no: 7, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	__/__/20__ [day/month/year]
Patient's age at sampling date (2/25)	[ ] same as at informed consent (___ years) or ___ years
IPTH (3/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Calcium (4/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Phosphate (5/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Alk. phosphatase (6/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
pH serum (7/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
C-reactive protein (CRP) (8/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Creatinine (9/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Albumin (10/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Sodium (11/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Potassium (12/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Chloride (13/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Magnesium (14/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

GOT (AST) (15/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
GPT (ALT) (16/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Gamma-GT (17/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Amylase (18/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Lipase (19/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
Urea (20/25)	_____.____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]

Uric acid (21/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
1,25-Dihydroxy-Vitamine D (22/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
25-Hydroxy-Vitamin D (23/25)	_____._____ _____ [ ] not available if outside normal limits - clinically relevant ? [[yes no]] if clinically relevant - causal relationship with: [[underlying disease medical history other]]
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____

Wound, pain and other assessments [Instance-no: 7, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/7)	[[yes no]]
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/7)	[[yes no]] if yes - degree of pain: ___ mm
Pregnancy test	
Pregnancy test (3/7)	[[positive negative not done not applicable (e.g. menopause, hysterectomy)]] Date:__/__/20__ [day/month/year]
Bone Mineral Density	
Has bone mineral density been assessed (4/7)	[[yes no]] if yes: method:[[DEXA scan CT]] t-score:__.__ z-score:__.__
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (5/7)	[[yes no]] if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: [[normal, not at all ill borderline mentally ill mildly ill moderately ill markedly ill severely ill extremely ill]]
Was the clinical global impression improvement assessed using the CGI-I-score (6/7)	[[yes no]] if yes: Compared to the patient’s condition at the baseline visit (V0), this patient’s condition is: [[very much improved since the initiation of treatment much improved minimally improved no change from baseline (the initiation of treatment) minimally worse much worse very much worse since the initiation of treatment]]
Comments (7/7)	_____ _____ _____

Study medication

Study medication [CRF-page 10/17] - Table	
Dosage (1/5)	___.__ g _ times a week
Dosage start date (2/5)	__/__/20__ [day/month/year]
Dosage stop date (3/5)	__/__/20__ [day/month/year] or [ ] currently ongoing
Number of administrations with this dosage (4/5)	___
Comments (5/5)	_____ _____ _____

Lesions

Lesions [CRF-page 11/17] - Table	
Lesion (1/25)	Lesion number: __ Lesion location: _____
Date of occurrence (2/25)	__/__/20__ [day/month/year] or [ ] before study start
Date of healing (3/25)	__/__/20__ [day/month/year] or [ ] still present
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: __/__/20__ [day/month/year] or [[not applicable (lesion not present at date of visit) no photodocumentation done]]

Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: [[0 1 2 3 4]] Depth: [[0 1 2 3 4]] Necrotic tissue type: [[0 1 2 3 4]] Total amount of necrotic tissue: [[0 1 2 3 4]] Granulation tissue type: [[0 1 2 3 4]] Total amount of granulation tissue: [[0 1 2 3 4]] Edges: [[0 1 2 3 4]] Periulcer skin viability: [[0 1 2 3 4]] Total score: __

Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: [[0 1 2 3 4]] Depth: [[0 1 2 3 4]] Necrotic tissue type: [[0 1 2 3 4]] Total amount of necrotic tissue: [[0 1 2 3 4]] Granulation tissue type: [[0 1 2 3 4]] Total amount of granulation tissue: [[0 1 2 3 4]] Edges: [[0 1 2 3 4]] Periulcer skin viability: [[0 1 2 3 4]] Total score: __
Photodocumentation V0 (7/25)	Date: __/__/20__ [day/month/year] or [[not applicable (lesion not present at date of visit) no photodocumentation done]]

Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: [[0 1 2 3 4]] Depth: [[0 1 2 3 4]] Necrotic tissue type: [[0 1 2 3 4]] Total amount of necrotic tissue: [[0 1 2 3 4]] Granulation tissue type: [[0 1 2 3 4]] Total amount of granulation tissue: [[0 1 2 3 4]] Edges: [[0 1 2 3 4]] Periulcer skin viability: [[0 1 2 3 4]] Total score: __

Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: [[0 1 2 3 4]] Depth: [[0 1 2 3 4]] Necrotic tissue type: [[0 1 2 3 4]] Total amount of necrotic tissue: [[0 1 2 3 4]] Granulation tissue type: [[0 1 2 3 4]] Total amount of granulation tissue: [[0 1 2 3 4]] Edges: [[0 1 2 3 4]] Periulcer skin viability: [[0 1 2 3 4]] Total score: __
Photodocumentation V2 (10/25)	Date: __/__/20__ [day/month/year] or [[not applicable (lesion not present at date of visit) no photodocumentation done]]

Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: [[0 1 2 3 4]] Depth: [[0 1 2 3 4]] Necrotic tissue type: [[0 1 2 3 4]] Total amount of necrotic tissue: [[0 1 2 3 4]] Granulation tissue type: [[0 1 2 3 4]] Total amount of granulation tissue: [[0 1 2 3 4]] Edges: [[0 1 2 3 4]] Periulcer skin viability: [[0 1 2 3 4]] Total score: __

Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: [[0 1 2 3 4]] Depth: [[0 1 2 3 4]] Necrotic tissue type: [[0 1 2 3 4]] Total amount of necrotic tissue: [[0 1 2 3 4]] Granulation tissue type: [[0 1 2 3 4]] Total amount of granulation tissue: [[0 1 2 3 4]] Edges: [[0 1 2 3 4]] Periulcer skin viability: [[0 1 2 3 4]] Total score: __
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or [[not applicable (lesion not present at date of visit) no photodocumentation done]]

Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: [[0 1 2 3 4]] Depth: [[0 1 2 3 4]] Necrotic tissue type: [[0 1 2 3 4]] Total amount of necrotic tissue: [[0 1 2 3 4]] Granulation tissue type: [[0 1 2 3 4]] Total amount of granulation tissue: [[0 1 2 3 4]] Edges: [[0 1 2 3 4]] Periulcer skin viability: [[0 1 2 3 4]] Total score: __

Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: [[0 1 2 3 4]] Depth: [[0 1 2 3 4]] Necrotic tissue type: [[0 1 2 3 4]] Total amount of necrotic tissue: [[0 1 2 3 4]] Granulation tissue type: [[0 1 2 3 4]] Total amount of granulation tissue: [[0 1 2 3 4]] Edges: [[0 1 2 3 4]] Periulcer skin viability: [[0 1 2 3 4]] Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or [[not applicable (lesion not present at date of visit) no photodocumentation done]]

Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: [[0 1 2 3 4]] Depth: [[0 1 2 3 4]] Necrotic tissue type: [[0 1 2 3 4]] Total amount of necrotic tissue: [[0 1 2 3 4]] Granulation tissue type: [[0 1 2 3 4]] Total amount of granulation tissue: [[0 1 2 3 4]] Edges: [[0 1 2 3 4]] Periulcer skin viability: [[0 1 2 3 4]] Total score: __

Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: [[0 1 2 3 4]] Depth: [[0 1 2 3 4]] Necrotic tissue type: [[0 1 2 3 4]] Total amount of necrotic tissue: [[0 1 2 3 4]] Granulation tissue type: [[0 1 2 3 4]] Total amount of granulation tissue: [[0 1 2 3 4]] Edges: [[0 1 2 3 4]] Periulcer skin viability: [[0 1 2 3 4]] Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or [[not applicable (lesion not present at date of visit) no photodocumentation done]]

Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: [[0 1 2 3 4]] Depth: [[0 1 2 3 4]] Necrotic tissue type: [[0 1 2 3 4]] Total amount of necrotic tissue: [[0 1 2 3 4]] Granulation tissue type: [[0 1 2 3 4]] Total amount of granulation tissue: [[0 1 2 3 4]] Edges: [[0 1 2 3 4]] Periulcer skin viability: [[0 1 2 3 4]] Total score: __

Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: [[0 1 2 3 4]] Depth: [[0 1 2 3 4]] Necrotic tissue type: [[0 1 2 3 4]] Total amount of necrotic tissue: [[0 1 2 3 4]] Granulation tissue type: [[0 1 2 3 4]] Total amount of granulation tissue: [[0 1 2 3 4]] Edges: [[0 1 2 3 4]] Periulcer skin viability: [[0 1 2 3 4]] Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or [[not applicable (lesion not present at date of visit) no photodocumentation done]]

Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: [[0 1 2 3 4]] Depth: [[0 1 2 3 4]] Necrotic tissue type: [[0 1 2 3 4]] Total amount of necrotic tissue: [[0 1 2 3 4]] Granulation tissue type: [[0 1 2 3 4]] Total amount of granulation tissue: [[0 1 2 3 4]] Edges: [[0 1 2 3 4]] Periulcer skin viability: [[0 1 2 3 4]] Total score: __

Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: [[0 1 2 3 4]] Depth: [[0 1 2 3 4]] Necrotic tissue type: [[0 1 2 3 4]] Total amount of necrotic tissue: [[0 1 2 3 4]] Granulation tissue type: [[0 1 2 3 4]] Total amount of granulation tissue: [[0 1 2 3 4]] Edges: [[0 1 2 3 4]] Periulcer skin viability: [[0 1 2 3 4]] Total score: __
Comments (25/25)	_____ _____ _____

Follow-up telephone interviews

Follow-up telephone interviews [CRF-page 12/17] - Table

Follow-up telephone interview 1	
Patient status [Instance-no: 1, page 1/1]	
Date of telephone call (1/7)	__/__/20__ [day/month/year]
Survival status	
Patient alive (2/7)	[[yes no]]
Disease status	
Is the disease still present (3/7)	[[yes no]]
Continuation STS-treatment	
Has the patient received further STS-treatment since last visit (4/7)	[[yes no]]
Further treatment	
Any further or additional treatment (5/7)	[[yes no]]
New calciphylaxis medication	
Any new medication for treatment of calciphylaxis (6/7)	[[yes no]]
Comments (7/7)	_____ _____ _____

Follow-up telephone interview 2	
Patient status [Instance-no: 2, page 1/1]	
Date of telephone call (1/7)	__/__/20__ [day/month/year]
Survival status	
Patient alive (2/7)	[[yes no]]
Disease status	
Is the disease still present (3/7)	[[yes no]]
Continuation STS-treatment	
Has the patient received further STS-treatment since last visit (4/7)	[[yes no]]
Further treatment	
Any further or additional treatment (5/7)	[[yes no]]
New calciphylaxis medication	
Any new medication for treatment of calciphylaxis (6/7)	[[yes no]]
Comments (7/7)	_____ _____ _____

End of study

End of study [CRF-page 13/17]	
Date of study end (1/6)	__/__/20__ [day/month/year]
Has the patient been listed on a transplant waiting list (2/6)	[[yes no]] if yes, date: __/__/20__ [day/month/year]
Date of last contact when patient was alive (3/6)	__/__/20__ [day/month/year]
Reason of study end (4/6)	[[finished per protocol early discontinuation lost to follow-up screening failure death study closed other]] if early discontinuation, lost to follow-up or other - please specify: _____ _____ _____ if patient died - date of death: __/__/20__ [day/month/year] [ ] not available reason of death: [[underlying disease other]] if other reason - please specify: _____ _____ _____
Has all patient data been entered as far as possible and checked, all data can be set read-only (5/6)	[[yes no]]
Comments (6/6)	_____ _____ _____

Medical history, concomitant medication and procedures, adverse events

Medical history [CRF-page 14/17] - Table	
Condition (1/5)	_____
Start date (2/5)	__/__/____ [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or [[currently ongoing ongoing after final examination]]
Treated with medications at study start (4/5)	[[yes no]]
Comments (5/5)	_____ _____ _____

Concomitant medication [CRF-page 15/17] - Table	
Medication (Trade name) (1/8)	_____
Start date (2/8)	__/__/____ [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or [[currently ongoing ongoing after final examination dosage changed]]
Dose and frequency (4/8)	total daily dose and unit: _____ frequency: _____
Route of administration (5/8)	_____
Indication (6/8)	Medical history: [[(not available)]] or Adverse event: [[(not available)]] or Other: _____
Was the medication administered to treat pain (7/8)	[[yes no]]
Comments (8/8)	_____ _____ _____

Adverse event [CRF-page 16/17] - Table	
Adverse event (1/9)	_____
Start date (2/9)	__/__/20__ [day/month/year]
Severity (3/9)	[[mild moderate severe]]
Causal relationship to study treatment (4/9)	[[related probable possible unlikely not related not assessable]]
Serious adverse event (5/9)	[[yes no]] if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	[[Dose not changed Dose reduced Dose increased Drug withdrawn Unknown Not applicable]]
Countermeasures (7/9)	[ ] None [ ] Drug treatment [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	[[Recovered/resolved Recovering/resolving Not recovered/not resolved Recovered/resolved with sequelae Fatal unknown]] if recovered/resolved or recovered/resolved with sequelae - please provide stop date: __/__/20__ [day/month/year]
Comments (9/9)	_____ _____ _____

Concomitant procedure/measure [CRF-page 17/17] - Table	
Procedure (1/5)	_____
Start date (2/5)	__/__/____ [day/month/year]
End date (3/5)	__/__/____ [day/month/year] or [[currently ongoing ongoing after final examination]]
Indication (4/5)	Medical history/concomitant disease: [[(not available)]] or Adverse event: [[(not available)]] or Other: _____
Comments (5/5)	_____ _____ _____

I confirm that I have carefully examined all entries of this patient. All information entered by myself or my colleagues is, to the best of my knowledge, correct as of the date below

Date:_____

Signature and stamp of investigator:_____

16.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority)

Protocol #: STS-CSM-1/13
Celerion Study #: CA20347
Country: AT/CH/GER
Investigator / Site #: N/A

Applicability:

☐ **Investigator Site File (ISF)**	**ISF filing location:**	
☐ **Trial Master File (TMF)**	**TMF filing location:**	
☒ **Other, specify**	**Filing location:**	Clinical Study Report - Appendix

Topic:

Listing of involved ECs and RAs

Detailed Description:

Austria:
Regulatory Authority:
Bundesamt für Sicherheit im Gesundheitswesen (BASG)/ Österreichische Agentur für Gesundheit und Ernährungssicherheit (AGES)

Ethics Committees:
Lead EC: Ethikkommission der Medizinischen Universität Graz
Local ECs: Ethikkommission des Landes Vorarlberg
Ethikkommission der Medizinischen Universität Wien
Ethikkommission für das Bundesland Salzburg

Switzerland:
Regulatory Authority: Swissmedic
Ethics Committee: Swissethics

Germany:
Regulatory Authority:
Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)

(Lead) Ethics Committee:
Ethik-Kommission bei der Landesärztekammer Baden-Württemberg

Author:			
Christine Drexhage	CRA	16-Jan-2018	
Printed Name	**Role/Title**	**Date** (dd-Mmm-yyyy)	**Signature**
Confirmed by:		☒ **N/A (for information only, no confirmation required)**	
Printed Name	**Role/Title**	**Date** (dd-Mmm-yyyy)	**Signature**

Note to File (NtF), Study Specific Template for CA20347,
Template version 1.0, Eff. Date 16-Dec-2016

Template Page 1 of 1

16.1.4 List and description of investigators and other important participants in the study

See Section 6 for a list of investigators and important participants in the study.

16.1.5 Signatures of principal or coordinating investigator(s) or sponsor’s responsible medical officer, depending on the regulatory authority's requirement.

See page 2 of the main document.

16.1.6 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used

Not applicable.

16.1.7 Randomization scheme and codes (subject identification and treatment assigned)

Not applicable.

16.1.8 Audit certificates

Not applicable, because there were no audits performed during the study.

16.1.9 Documentation of statistical methods

Not applicable.

16.1.10 Documentation of inter-laboratory standardisation methods and quality assurance procedures if used

The following documents are included in this section:

- Laboratory Normal Ranges for site 102, 103 and 104

STS-CSM-[illegible]_13 - Registered Normal Ranges of Site [0102] Academic Teaching Hospital Feldkirch
(Report ge[illegible]erated on: 18SEP18)

	Parameter	Valid as of	Valid from starting age	Unit	Lower limit female *	Upper limit female *	Lower limit male *	Upper limit male *
1,25-Dihydr[illegible]y-Vitamine D		Study start	0	NG/L	23	93	23	93
25-Hydroxy-[illegible]itamin D		Study start	0	UG/L	20	100	20	100
Albumin		Study start	0	G/DL	3.5	5.2	3.5	5.2
Alk. phospha[illegible]ase		Study start	0	U/L	35	105	40	130
Amylase		Study start	0	U/L	28	100	28	100
Bicarbonate		Study start	0	MMOL/L	21	26	21	26
C-reactive p[illegible]tein (CRP)		Study start	0	MG/DL	NA	0.499	NA	0.499
Calcium		Study start	0	MMOL/L	2.15	2.55	2.15	2.55
Chloride		Study start	0	MMOL/L	98	107	98	107
Creatinine		Study start	0	MG/DL	0.5	0.9	0.7	1.2
GOT (AST)		Study start	0	U/L	NA	34.99	NA	49.99
GPT (ALT)		Study start	0	U/L	NA	34.99	NA	49.99
Gamma-GT		Study start	0	U/L	NA	39.99	NA	59.99
Hemoglobin		Study start	0	G/L	123	158	144	175
iPTH		Study start	0	PG/ML	15	65	15	65
Lipase		Study start	0	U/L	NA	59.99	NA	59.99
Magnesium		Study start	0	MMOL/L	0.66	1.07	0.66	1.07
Oxygen satu[illegible]tion		Study start	0	%	70	80	70	80
Partial pressu[illegible]e of oxygen		Study start	0	MMHG	65	100	65	100
Partial pressu[illegible]e of oxygen venous		Study start	0	MMHG	34	44	34	44
Phosphate		Study start	0	MMOL/L	0.81	1.45	0.81	1.45
Potassium		Study start	0	MMOL/L	3.5	5.1	3.5	5.1
Sodium		Study start	0	MMOL/L	136	145	136	145
Urea		Study start	0	MG/DL	17	49	17	49
Uric acid		Study start	0	MG/DL	2.4	5.7	3.4	7
White blood c[illegible]lls		Study start	0	G/L	3.7	10	3.7	10
pH serum		Study start	0	1/1	7.35	7.43	7.35	7.43

STS-CSM-1_13 - Registered Normal Ranges of Site [0102] Academic Teaching Hospital Feldkirch
(Report generated on: 18SEP18)

Parameter	Valid as of	Valid from starting age	Unit	Lower limit female *	Upper limit female *	Lower limit male *	Upper limit male *

NA: no limit available.
*: Limits are still part of the normal range.

I hereby confirm that these reference ranges are valid for study STS-CSM-1_13.

Name (capital letters): GSTACH TANJA

Date: 19.9.18

Signature: Gstach Tanja

STS-CSM-1_13 - Registered Normal Ranges of Site [0103] Medical University of Vienna
[Report generated on: 31AUG18]

Parameter	Values of standard	Unit	Lower limit females	Upper limit females	Lower limit males	Upper limit males
1,25-Dihydroxy-Vitamine D	Study start	PG/ML	19.9	79.3	19.9	79.3
25-Hydroxy-Vitamin D	Study start	NMOL/L	75	250	75	250
Albumin	Study start	G/L	35	52	35	52
Alk. phosphatase	Study start	U/L	35	105	40	130
Amylase	Study start	U/L	28	100	28	100
Bicarbonate	Study start	MMOL/L	22	31	24	31
C-reactive protein (CRP)	Study start	MG/DL	NA	0.499	NA	0.499
Calcium	Study start	MMOL/L	2.15	2.5	2.15	2.5
	Study start	MMOL/L	2.2	2.55	2.2	2.55
Chloride	Study start	MMOL/L	98	107	98	107
Creatinine	Study start	MG/DL	0.5	0.9	0.7	1.2
GOT (AST)	Study start	U/L	NA	34.99	NA	49.99
GPT (ALT)	Study start	U/L	NA	34.98	NA	49.99
Gamma-GT	Study start	U/L	NA	39.99	NA	59.99
Hemoglobin	Study start	G/DL	12	16	13.5	18
IPTH	Study start	PG/ML	15	65	15	65
Lipase	Study start	U/L	13	60	13	60
Magnesium	Study start	MMOL/L	0.66	1.07	0.66	1.07
Oxygen saturation	Study start	%	65	80	65	80
Partial pressure of oxygen	Study start	MMHG	83	108	83	108
Partial pressure of oxygen venous	Study start	MMHG	36	44	36	44
Phosphate	Study start	MMOL/L	0.81	1.45	0.81	1.45
Potassium	Study start	MMOL/L	3.5	5.1	3.5	5.1
Sodium	Study start	MMOL/L	136	145	136	145
Urea	Study start	MG/DL	6	20	6	20
	Study start	MG/DL	8	23	8	23
Uric acid	Study start	MG/DL	2.4	5.7	3.4	7
White blood cells	Study start	G/L	4	10	4	10
pH serum	Study start	1/1	7.35	7.45	7.35	7.45

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STS-CSM-1_13 - Registered Normal Ranges of Site [0103] Medical University of Vienna
(Report generated on: 31AUG18)

Parameter	Value from (start to age)	Unit	Lower limit female	Upper limit female	Lower limit male	Upper limit male
NA! no limit available / Limits are still part of the normal range						

I hereby confirm that these reference ranges are valid for study STS-CSM-1_13.

Name (capital letters): BENJAMIN SCHAIRER

Date: 10.9.18

Signature: Schair

STS-CSM-1_13 - Registered Normal Ranges of Site [0104] Universitätsklinikum Salzburg
(Report generated on: 18SEP18)

Parameter	Valid as of	Valid from starting age	Unit	Lower limit female *	Upper limit female *	Lower limit male *	Upper limit male *
1,25-Dihydroxy-Vitamine D	Study start	0	PG/ML	19.9	79.3	19.9	79.3
25-Hydroxy-Vitamin D	Study start	0	NG/ML	20.01	NA	20.01	NA
Albumin	Study start	0	G/DL	3.4	5	3.4	5
Alk. phosphatase	Study start	0	U/L	35	104	40	129
Amylase	Study start	0	U/L	28	100	28	100
Bicarbonate	Study start	0	MMOL/L	21	28	21	28
C-reactive protein (CRP)	Study start	0	MG/DL	NA	0.599	NA	0.599
Calcium	Study start	0	MMOL/L	2.13	2.63	2.13	2.63
Chloride	Study start	0	MMOL/L	97	108	97	108
Creatinine	Study start	0	MG/DL	0.5	1.1	0.6	1.2
GOT (AST)	Study start	0	U/L	10	35	10	50
GPT (ALT)	Study start	0	U/L	10	35	10	50
Gamma-GT	Study start	0	U/L	5	39	10	66
Hemoglobin	Study start	0	G/DL	12	16	13.5	17.7
IPTH	Study start	0	NG/L	15	65	15	65
Lipase	Study start	0	U/L	13	60	13	60
Magnesium	Study start	0	MMOL/L	0.77	1.03	0.73	1.06
Oxygen saturation	Study start	0	%	20	60	20	60
Partial pressure of oxygen	Study start	0	MMHG	60	100	60	100
Partial pressure of oxygen venous	Study start	0	MMHG	30	40	30	40
Phosphate	Study start	0	MMOL/L	0.65	1.3	0.65	1.3
Potassium	Study start	0	MMOL/L	3.6	5	3.6	5
Sodium	Study start	0	MMOL/L	135	148	135	148
Urea	Study start	0	MG/DL	10	40	10	50
Uric acid	Study start	0	MG/DL	2	6.4	3.5	7
White blood cells	Study start	0	G/L	3.5	9.8	3.5	9.8
pH serum	Study start	0	1/1	7.35	7.45	7.35	7.45

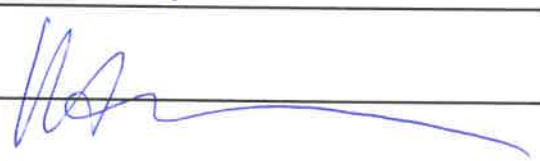
STS-CSM-1_13 - Registered Normal Ranges of Site [0104] Universitätsklinikum Salzburg
(Report generated on: 18SEP18)

Parameter	Valid as of	Valid from starting age	Unit	Lower limit female *	Upper limit female *	Lower limit male *	Upper limit male *
NA: no limit available. *: Limits are still part of the normal range.							

I hereby confirm that these reference ranges are valid for study STS-CSM-1_13.

Name (capital letters): Dr. H. SALMHOFER

Date: 20.9.18

Signature: 

16.1.11 Publications based on the study

Not applicable.

16.1.12 Important publications referenced in the report

Not applicable.

16.2 *Subject Data Listings*

Not applicable, see Section 16.3 for patient data.

16.3 *Case Report Forms*

Study STS-CSM-1/13, Center: Academic Teaching Hospital Feldkirch [0102]
Patient No. 1: CRF Hardcopy, 18.09.2018 , 12:56:45

Screening/Start of run-in phase [14.04.2016]

Demographic information [CRF-page 1/17]	
Date of written informed consent (1/5)	**14**/**04**/20**16** [day/month/year]
Patient ID (2/5)	**01**-**02**-**001** (country-site-patient)
Patient year of birth (3/5)	19**33** [year] Age (at date of informed consent): **82** years
Gender (4/5)	**male**
Race of patient (5/5)	**white** if other - please specify: _____ _____ _____

Inclusion/exclusion criteria [CRF-page 2/17]	
Inclusion criteria	
Patient ⩾ 18 years (1/11)	**yes**
Male or female HD patients with a diagnosis of calciphylaxis (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching) (2/11)	**yes**
Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study (3/11)	**yes**
Exclusion criteria	
Sodium metabisulfite hypersensitivity, among others the history of bronchial asthma due to known sodium metabisulfite hypersensitivity (4/11)	**no**
Patients who have participated in any other investigational studies within 30 days previous to enrollment (5/11)	**no**
History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment (6/11)	**no**
Good response to conventional treatment (7/11)	**no**
Life expectancy less than 4 months in the judgement of the investigator (8/11)	**no**
Comments (9/11)	_____ _____ _____

Clinical examination [CRF-page 3/17]	
Vital signs	
Date of assessment (1/24)	**14**/**04**/20**16** [day/month/year]
Body height (2/24)	**155** cm
Body weight (3/24)	**57.2** kg
Blood pressure (measured after patient has rested for 5 minutes) (4/24)	**106** mmHg / **65** mmHg [systolic/diastolic]
Heart rate (measured after patient has rested for 5 minutes) (5/24)	**70** b/min
BMI (calculated) (6/24)	**23.8** kg/m²
12-lead ECG	
ECG findings (7/24)	Date: **14**/**04**/20**16** [day/month/year] Result: **normal** if abnormal and clinically relevant - please specify: _____ _____

	_____
Physical examination	
Were physical examinations performed (8/24)	**yes** if yes - date: **14**/**04**/20**16** [day/month/year]
Head (9/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (10/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (11/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Dermatological (12/24)	**abnormal** if abnormal - please specify: **Calciphylaxie** if abnormal - clinically relevant: **no**
Musculosceletal (13/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (14/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (15/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Neurological (16/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
	not done if normal or abnormal - please specify:

Other (17/24)	_____ _____ _____ if abnormal - clinically relevant: ___
Calciphylaxis diagnosis	
Calciphylaxis diagnosed according to typical signs and symptoms (18/24)	**yes** if yes - please check all that apply: **[x] Severe pain** **[x] Livedo** **[x] Violaceous plaques** [ ] Ulcerations **[x] Necroses** if ulcerations and/or necroses - have other causes been excluded: **yes**
Tobacco use	
Tobacco use (19/24)	**Non-smoker**
Checklist	
Does the patient have any relevant medical history or concomitant diseases (20/24)	**yes**
Does the patient receive any concomitant medication (including pain medication) (21/24)	**yes**
Any concomitant procedures/measures performed (22/24)	**yes**
Has sample for biobanking been taken (23/24)	**yes** if yes - date: **14**/**04**/20**16** [day/month/year]
Comments (24/24)	_____ _____ _____

Hematology and venous blood gas analysis [CRF-page 4/17]	
Hematology	
Date of sample (1/12)	**14**/**04**/20**16** [day/month/year]
Patient's age at sampling date (2/12)	**[x] same as at informed consent** (**82** years) or ___ years
Hemoglobin (3/12)	**107 g/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
White blood cells (4/12)	**7.3 G/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min **[x] not available**
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____.____ **mmHg** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Partial pressure of oxygen venous (8/12)	**40 mmHg** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Oxygen saturation (9/12)	**73.4 %** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
	21.5 mmol/l

Bicarbonate (10/12)	if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	_____ _____ _____

Clinical chemistry [CRF-page 5/17]	
Clinical Chemistry	
Date of sample (1/25)	**14**/**04**/20**16** [day/month/year]
Patient's age at sampling date (2/25)	**[x] same as at informed consent** (**82** years) or ___ years
IPTH (3/25)	**148 pg/ml** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Calcium (4/25)	**2.11 mmol/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Phosphate (5/25)	**1.67 mmol/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Alk. phosphatase (6/25)	**135 U/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
pH serum (7/25)	**7.34 1/1** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	**1.94 mg/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Creatinine (9/25)	**4.4 mg/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Albumin (10/25)	**2.7 g/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Sodium (11/25)	**136 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Potassium (12/25)	**4.1 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Chloride (13/25)	**98 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Magnesium (14/25)	**0.77 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
	27 U/l

GOT (AST) (15/25)	if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GPT (ALT) (16/25)	**14 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Gamma-GT (17/25)	**55 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Amylase (18/25)	**88 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Lipase (19/25)	**6 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Urea (20/25)	**66 mg/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Uric acid (21/25)	**4.9 mg/dl** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	**17.6 ng/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
25-Hydroxy-Vitamin D (23/25)	**16 ug/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____

Wound, pain and other assessments [CRF-page 6/17]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/4)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/4)	**yes** if yes - degree of pain: **32** mm
Comments (3/4)	_____ _____ _____

End of run-in phase

Inclusion/exclusion criteria [CRF-page 7/17]	
Inclusion criteria	
Patient $\geqslant$ 18 years (1/11)	**yes**
Male or female HD patients with a diagnosis of calciphylaxis. (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching). (2/11)	**yes**
Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study	**yes**

(3/11)	
Exclusion criteria	
Sodium metabisulfite hypersensitivity, among others the history of bronchial asthma due to known sodium metabisulfite hypersensitivity (4/11)	**no**
Patients who have participated in any other investigational studies within 30 days previous to enrollment (5/11)	**no**
History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment (6/11)	**no**
Good response to conventional treatment (7/11)	**no**
Life expectancy less than 4 months in the judgement of the investigator (8/11)	**no**
Comments (9/11)	_____ _____ _____

Completion of run-in-phase [CRF-page 8/17]	
Has a skin biopsy been taken (1/7)	**yes** if yes, date:**14**/**04**/20**16** [day/month/year] if yes - calciphylaxis diagnosis confirmed by analysis: **yes**
Has the patient agreed to participate in the clinical trial and to undergo STS treatment (2/7)	**yes**
Disease status under BSC (3/7)	**rapidly progressive disease**
Have all screening/baseline assessments been performed and is patient considered eligible for treatment start (4/7)	**yes** if no - please check all that apply: [ ] patient did not meet all in-/exclusion criteria [ ] withdrawal of informed consent by the patient [ ] discretion of the investigator [ ] calciphylaxis diagnosis not confirmed [ ] other reason if other reason - please specify: _____ _____ _____
Comments (5/7)	_____ _____ _____

Visits

Visits [CRF-page 9/17] - Table	
Instance-no: 1 (Visits)	
Visit 0 Start of visit [Instance-no: 1, page 1/5]	
Actual date of visit (1/6)	**19**/**04**/20**16** [day/month/year] [ ] not done
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (2/6)	**no**
Any new concomitant procedures/measures or changes in concomitant procedures/measures (3/6)	**no**
Any new adverse events or changes in adverse events (4/6)	**no**
Soft tissue radiographs	
Have soft tissue radiographs been taken (optional) (5/6)	**yes** if yes, date: **04**/**04**/20**16** [day/month/year]
Comments (6/6)	**date is correct**
Clinical examination [Instance-no: 1, page 2/5]	

Vital signs	
Date of assessment (1/17)	**19**/**04**/20**16** [day/month/year]
Body weight (2/17)	**58.7** kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	**148** mmHg / **88** mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	**61** b/min [ ] not done
BMI (calculated) (5/17)	**24.4** kg/m²
Physical examination	
Were physical examinations performed (6/17)	**yes** if yes - date: **19**/**04**/20**16** [day/month/year]
Head (7/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (8/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (9/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Dermatological (10/17)	**abnormal** if abnormal - please specify: **Calciphylaxis** if abnormal - clinically relevant: **no**
Musculosceletal (11/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (12/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (13/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
	normal if abnormal - please specify:

Neurological (14/17)	_____ _____ _____ if abnormal - clinically relevant: ___
Other (15/17)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Biobanking	
Has sample for biobanking been taken (16/17)	**yes** if yes - date: **19**/**04**/20**16** [day/month/year]
Comments (17/17)	_____ _____ _____
Hematology and venous blood gas analysis [Instance-no: 1, page 3/5]	
Hematology	
Date of sample (1/12)	**19**/**04**/20**16** [day/month/year]
Patient's age at sampling date (2/12)	**[x] same as at informed consent** (**82** years) or ___ years
Hemoglobin (3/12)	**97 g/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
White blood cells (4/12)	**4.2 G/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min [ ] not available
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____.____ **mmHg [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Partial pressure of oxygen venous (8/12)	**44.6 mmHg** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Oxygen saturation (9/12)	**81 %** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Bicarbonate (10/12)	**24.1 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	_____ _____ _____
Clinical chemistry [Instance-no: 1, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	**19**/**04**/20**16** [day/month/year]
	[x] same as at informed consent (**82** years)

Patient's age at sampling date (2/25)	or ___ years
IPTH (3/25)	**139 pg/ml** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Calcium (4/25)	**1.97 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Phosphate (5/25)	**1.21 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Alk. phosphatase (6/25)	**138 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
pH serum (7/25)	**7.38 1/1** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	**3.68 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Creatinine (9/25)	**3.5 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Albumin (10/25)	**2.4 g/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Sodium (11/25)	**140 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Potassium (12/25)	**4.2 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Chloride (13/25)	**102 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Magnesium (14/25)	**0.74 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GOT (AST) (15/25)	**21 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GPT (ALT) (16/25)	**10 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Gamma-GT (17/25)	**57 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Amylase (18/25)	**83 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____

Lipase (19/25)	**7 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Urea (20/25)	**57 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Uric acid (21/25)	**3.6 mg/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	**28.3 ng/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
25-Hydroxy-Vitamin D (23/25)	**14 ug/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____
Wound, pain and other assessments [Instance-no: 1, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	**yes** if yes - degree of pain: **58** mm
Bone Mineral Density	
Has bone mineral density been assessed (3/6)	**yes** if yes: method:**DEXA scan** t-score:**-4** z-score:**-2.5**
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (4/6)	**yes** if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: **markedly ill**
Comments (5/6)	_____ _____ _____

Instance-no: 2 (Visits)

Visit 1 Start of visit [Instance-no: 2, page 1/3]	
Planned date of visit (1/7)	17/05/2016 [day/month/year]
Actual date of visit (2/7)	**17**/**05**/20**16** [day/month/year] [ ] not done if deviation from planned date - please provide reason: _____ _____ _____
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	**yes**
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	**no**

Any new adverse events or changes in adverse events (5/7)	**yes**
Any new lesions under STS treatment (6/7)	**no**
Comments (7/7)	_____ _____ _____
Clinical examination [Instance-no: 2, page 2/3]	
Vital signs	
Date of assessment (1/16)	**17**/**05**/20**16** [day/month/year]
Body weight (2/16)	**53** kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/16)	**132** mmHg / **75** mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/16)	**61** b/min [ ] not done
BMI (calculated) (5/16)	**22.1** kg/m²
Physical examination	
Were physical examinations performed (6/16)	**yes** if yes - date: **17**/**05**/20**16** [day/month/year]
Head (7/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (8/16)	**abnormal** if abnormal - please specify: **Otitis media right** if abnormal - clinically relevant: **yes**
Cardiovascular (9/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Dermatological (10/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Musculosceletal (11/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (12/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
	normal if abnormal - please specify:

Gastrointestinal (13/16)	_____ _____ _____ if abnormal - clinically relevant: ___
Neurological (14/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Other (15/16)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Comments (16/16)	**Otitis media right**
Wound, pain and other assessments [Instance-no: 2, page 3/3]	
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (1/5)	**yes** if yes - degree of pain: **48** mm
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (2/5)	**yes** if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: **moderately ill**
Was the clinical global impression improvement assessed using the CGI-I-score (3/5)	**yes** if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: **minimally improved**
Comments (4/5)	_____ _____ _____
Instance-no: 3 (Visits)	
Visit 2 Start of visit [Instance-no: 3, page 1/5]	
Planned date of visit (1/7)	14/06/2016 [day/month/year]
Actual date of visit (2/7)	**14**/**06**/20**16** [day/month/year] [ ] not done if deviation from planned date - please provide reason: _____ _____ _____
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	**yes**
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	**no**
Any new adverse events or changes in adverse events (5/7)	**no**
Any new lesions under STS treatment (6/7)	**no**
Comments (7/7)	_____ _____ _____
Clinical examination [Instance-no: 3, page 2/5]	
Vital signs	

Date of assessment (1/17)	**14**/**06**/20**16** [day/month/year]
Body weight (2/17)	**50** kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	**111** mmHg / **70** mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	**68** b/min [ ] not done
BMI (calculated) (5/17)	**20.8** kg/m²
Physical examination	
Were physical examinations performed (6/17)	**yes** if yes - date: **14**/**06**/20**16** [day/month/year]
Head (7/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (8/17)	**abnormal** if abnormal - please specify: **Hämatom - peri-orbital left** if abnormal - clinically relevant: **no**
Cardiovascular (9/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Dermatological (10/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Musculosceletal (11/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (12/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (13/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
	normal if abnormal - please specify: _____

Neurological (14/17)	_____ _____ if abnormal - clinically relevant: ___
Other (15/17)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Biobanking	
Has sample for biobanking been taken (16/17)	**yes** if yes - date: **14**/**06**/20**16** [day/month/year]
Comments (17/17)	_____ _____ _____
Hematology and venous blood gas analysis [Instance-no: 3, page 3/5]	
Hematology	
Date of sample (1/12)	**14**/**06**/20**16** [day/month/year]
Patient's age at sampling date (2/12)	**[x] same as at informed consent** (**82** years) or ___ years
Hemoglobin (3/12)	**95 g/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
White blood cells (4/12)	**4.3 G/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min **[x] not available**
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____.____ **mmHg [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Partial pressure of oxygen venous (8/12)	**40.1 mmHg** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Oxygen saturation (9/12)	**67.7 %** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Bicarbonate (10/12)	**19.2 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	_____ _____ _____
Clinical chemistry [Instance-no: 3, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	**14**/**06**/20**16** [day/month/year]
Patient's age at sampling date (2/25)	**[x] same as at informed consent** (**82** years) or ___ years

IPTH (3/25)	**148 pg/ml** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Calcium (4/25)	**2.1 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Phosphate (5/25)	_____._____ **mmol/l [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Alk. phosphatase (6/25)	**158 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
pH serum (7/25)	**7.31 1/1** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	**1.8 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Creatinine (9/25)	**3.5 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Albumin (10/25)	**2.5 g/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Sodium (11/25)	**136 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Potassium (12/25)	**4 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Chloride (13/25)	**98 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Magnesium (14/25)	**0.72 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GOT (AST) (15/25)	**36 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GPT (ALT) (16/25)	**32 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Gamma-GT (17/25)	**64 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Amylase (18/25)	**84 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
	5 U/l [ ] not available

Lipase (19/25)	if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Urea (20/25)	**62 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Uric acid (21/25)	**4.1 mg/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	**0 ng/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
25-Hydroxy-Vitamin D (23/25)	**7 ug/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____
Wound, pain and other assessments [Instance-no: 3, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	**yes** if yes - degree of pain: **21** mm
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (3/6)	**yes** if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: **moderately ill**
Was the clinical global impression improvement assessed using the CGI-I-score (4/6)	**yes** if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: **much improved**
Comments (5/6)	_____ _____ _____

Instance-no: 4 (Visits)

Visit 3 Start of visit [Instance-no: 4, page 1/5]	
Planned date of visit (1/7)	09/08/2016 [day/month/year]
Actual date of visit (2/7)	__/__/20__ [day/month/year] [ ] not done if deviation from planned date - please provide reason: _____ _____ _____
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	___
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	___
Any new adverse events or changes in adverse events (5/7)	___
Any new lesions under STS treatment (6/7)	___

Comments (7/7)	_____ _____ _____
Clinical examination [Instance-no: 4, page 2/5]	
Vital signs	
Date of assessment (1/17)	__/__/20__ [day/month/year]
Body weight (2/17)	___._ kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	___ mmHg / ___ mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	___ b/min [ ] not done
BMI (calculated) (5/17)	___._ kg/m²
Physical examination	
Were physical examinations performed (6/17)	___ if yes - date: __/__/20__ [day/month/year]
Biobanking	
Has sample for biobanking been taken (7/17)	___ if yes - date: __/__/20__ [day/month/year]
Comments (8/17)	_____ _____ _____
Hematology and venous blood gas analysis [Instance-no: 4, page 3/5]	
Hematology	
Date of sample (1/12)	__/__/20__ [day/month/year]
Patient's age at sampling date (2/12)	[ ] same as at informed consent (___ years) or ___ years
Hemoglobin (3/12)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
White blood cells (4/12)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min [ ] not available
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Partial pressure of oxygen venous (8/12)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Oxygen saturation (9/12)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Bicarbonate (10/12)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	_____ _____ _____
Clinical chemistry [Instance-no: 4, page 4/5]	
Clinical Chemistry	

Date of sample (1/25)	__/__/20__ [day/month/year]
Patient's age at sampling date (2/25)	[ ] same as at informed consent (**82** years) or ___ years
IPTH (3/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Calcium (4/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Phosphate (5/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Alk. phosphatase (6/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
pH serum (7/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Creatinine (9/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Albumin (10/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Sodium (11/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Potassium (12/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Chloride (13/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Magnesium (14/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GOT (AST) (15/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GPT (ALT) (16/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Gamma-GT (17/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Amylase (18/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___

	if clinically relevant - causal relationship with: _____
Lipase (19/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Urea (20/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Uric acid (21/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
25-Hydroxy-Vitamin D (23/25)	_____._____ [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____
Wound, pain and other assessments [Instance-no: 4, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	___
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	___ if yes - degree of pain: ___ mm
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (3/6)	___ if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: _____
Was the clinical global impression improvement assessed using the CGI-I-score (4/6)	___ if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: _____
Comments (5/6)	_____ _____ _____

Study medication

Study medication [CRF-page 10/17] - Table	
Instance-no: 1 (Study Medication)	
Dosage (1/5)	**25** g **3** times a week
Dosage start date (2/5)	**19**/**04**/20**16** [day/month/year]
Dosage stop date (3/5)	**25**/**06**/20**16** [day/month/year] or [ ] currently ongoing
Number of administrations with this dosage (4/5)	**28**
Comments (5/5)	**09.06.2016 and 23.06.2016: no IMP Administration due to cancelled dialysis. According to the protocol the dose of 25g should be administered 30min before end of dialyses. However the Infusion start time were adjusted according to the patient tolerability to 60min before end of dialysis in some cases. The administration procedure were adapted**

	in accordance with the sponsor.

Instance-no: 2 (Study Medication)	
Dosage (1/6)	___.__ g _ times a week
Dosage start date (2/6)	__/__/20__ [day/month/year]
Dosage stop date (3/6)	__/__/20__ [day/month/year] or [ ] currently ongoing
Number of administrations with this dosage (4/6)	___
Reason for dosage change (5/6)	_____ _____ _____
Comments (6/6)	_____ _____ _____

Lesions

Lesions [CRF-page 11/17] - Table	
Instance-no: 1 (Lesions)	
Lesion (1/25)	Lesion number: **1** Lesion location: **right calf pretibial**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	__/__/20__ [day/month/year] or **[x] still present**
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **14**/**04**/20**16** [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: _ Periulcer skin viability: **2** Total score: **20**
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **13.07** cm^2 or [ ] Wound area not assessed Size: **3** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **4** Periulcer skin viability: **1**

	Total score: **26**
Photodocumentation V0 (7/25)	Date: **19**/**04**/20**16** [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0** cm^2 or [ ] Wound area not assessed Size: **4** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **3** Periulcer skin viability: **3** Total score: **28**
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **35.57** cm^2 or [ ] Wound area not assessed Size: **4** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **1** Total score: **25**
Photodocumentation V2 (10/25)	Date: **14**/**06**/20**16** [day/month/year] or _____
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **1.4** cm^2 or [ ] Wound area not assessed Size: **1** Depth: **1** Necrotic tissue type: **1** Total amount of necrotic tissue: **1** Granulation tissue type: **1** Total amount of granulation tissue: **1** Edges: **1** Periulcer skin viability: **3** Total score: **10**

Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **1** Depth: **1** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **1** Total amount of granulation tissue: **1** Edges: **1** Periulcer skin viability: **0** Total score: **5**
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
	Initials Dermatologist: _ / _ [first/last name]

Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size:

Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	_ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	**Photography VR (M/L): Edges is empty. Dermatologist was unable to specify.**
Instance-no: 2 (Lesions)	
Lesion (1/25)	Lesion number: **2** Lesion location: **right calf proximal**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**

Date of healing (3/25)	**14**/**06**/20**16** [day/month/year] or [ ] still present
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **14**/**04**/20**16** [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **11.8** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **2** Necrotic tissue type: **3** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: _ Periulcer skin viability: **2** Total score: **19**
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **13.07** cm^2 or [ ] Wound area not assessed Size: **3** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **4** Periulcer skin viability: **1** Total score: **26**
Photodocumentation V0 (7/25)	Date: **19**/**04**/20**16** [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0** cm^2 or [ ] Wound area not assessed Size: **4** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **3** Total amount of granulation tissue: **4** Edges: **3** Periulcer skin viability: **3**

	Total score: **27**
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **28** cm^2 or [ ] Wound area not assessed Size: **4** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **1** Total score: **25**
Photodocumentation V2 (10/25)	Date: **14**/**06**/20**16** [day/month/year] or _____
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **2** Total score: **2**
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **0** Total score: **0**
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**

Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed

Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size:

Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	_ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	**Photography VR (M/L): Edges is empty. Dermatologist was unable to specify.**

Instance-no: 3 (Lesions)

Lesion (1/25)	Lesion number: **3** Lesion location: **left distal lateral calf**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	__/__/20__ [day/month/year] or **[x] still present**
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **14**/**04**/20**16** [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0.24** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **2**

	Total score: **2**
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **0.18** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **1** Total score: **1**
Photodocumentation V0 (7/25)	Date: **19**/**04**/20**16** [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0.29** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **3** Total score: **3**
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **0.3** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **0** Total score: **20**
	Date: **14**/**06**/20**16** [day/month/year] or

Photodocumentation V2 (10/25)	_____
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **1** cm^2 or [ ] Wound area not assessed Size: **1** Depth: **1** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **1** Total amount of granulation tissue: **1** Edges: **1** Periulcer skin viability: **2** Total score: **7**
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **1.08** cm^2 or [ ] Wound area not assessed Size: **1** Depth: **1** Necrotic tissue type: **1** Total amount of necrotic tissue: **1** Granulation tissue type: **3** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **0** Total score: **13**
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed

Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed

Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth:

Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	_ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	_____ _____ _____

Instance-no: 4 (Lesions)

Lesion (1/25)	Lesion number: **4** Lesion location: **left distal medial calf**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	**14**/**06**/20**16** [day/month/year] or [ ] still present
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **14**/**04**/20**16** [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **1.4** cm^2 or [ ] Wound area not assessed Size: **1** Depth: **1** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **1** Total amount of granulation tissue: **1** Edges: **1** Periulcer skin viability: **2** Total score: **7**
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **0**

	Total score: **0**
Photodocumentation V0 (7/25)	Date: **19**/**04**/20**16** [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0.7** cm^2 or [ ] Wound area not assessed Size: **1** Depth: **1** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **1** Total amount of granulation tissue: **1** Edges: **1** Periulcer skin viability: **2** Total score: **7**
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **1.4** cm^2 or [ ] Wound area not assessed Size: **1** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **0** Total score: **1**
Photodocumentation V2 (10/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __

Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
	Initials Dermatologist: _ / _ [first/last name]

Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size:

Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	_ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	_____ _____ _____
Instance-no: 5 (Lesions)	
Lesion (1/25)	Lesion number: __ Lesion location: _____

Date of occurrence (2/25)	__/__/20__ [day/month/year] or [ ] before study start
Date of healing (3/25)	__/__/20__ [day/month/year] or [ ] still present
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V0 (7/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _

	Total score: __
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V2 (10/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Date: __/__/20__ [day/month/year] or

Photodocumentation V3 (13/25)	_____
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed

Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or _____
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed

Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	_____ _____ _____

Follow-up telephone interviews

Follow-up telephone interviews [CRF-page 12/17] - Table	
Instance-no: 1 (Follow-up telephone interviews)	
Follow-up telephone interview 1 Patient status [Instance-no: 1, page 1/1]	
Date of telephone call (1/7)	**18**/**08**/20**16** [day/month/year]
Survival status	
Patient alive (2/7)	**no**
Disease status	
Is the disease still present (3/7)	___
Continuation STS-treatment	
Has the patient received further STS-treatment since last visit (4/7)	**no**
Further treatment	
Any further or additional treatment (5/7)	**no**
New calciphylaxis medication	
Any new medication for treatment of calciphylaxis (6/7)	**no**
Comments (7/7)	**Date of death: 26.07.2016; disease status: UNK since last contact**
Instance-no: 2 (Follow-up telephone interviews)	

Follow-up telephone interview 2 Patient status [Instance-no: 2, page 1/1]	
Date of telephone call (1/7)	__/__/20__ [day/month/year]
Survival status	
Patient alive (2/7)	___
Disease status	
Is the disease still present (3/7)	___
Continuation STS-treatment	
Has the patient received further STS-treatment since last visit (4/7)	___
Further treatment	
Any further or additional treatment (5/7)	___
New calciphylaxis medication	
Any new medication for treatment of calciphylaxis (6/7)	___
Comments (7/7)	_____ _____ _____

End of study [27.06.2016]

End of study [CRF-page 13/17]	
Date of study end (1/6)	**27**/**06**/20**16** [day/month/year]
Has the patient been listed on a transplant waiting list (2/6)	**no** if yes, date: __/__/20__ [day/month/year]
Date of last contact when patient was alive (3/6)	**27**/**06**/20**16** [day/month/year]
Reason of study end (4/6)	**early discontinuation** if early discontinuation, lost to follow-up or other - please specify: **discontinuation of hemodialysis due to Patient request.** if patient died - date of death: __/__/20__ [day/month/year] [ ] not available reason of death: _____ if other reason - please specify: _____ _____ _____
Has all patient data been entered as far as possible and checked, all data can be set read-only (5/6)	**yes**
Comments (6/6)	_____ _____ _____

Medical history, concomitant medication and procedures, adverse events

Medical history [CRF-page 14/17] - Table	
Instance-no: 1 (Medical History)	
Condition (1/5)	**Renal Hyperparathyreoidism**
Start date (2/5)	**30**/**04**/**2014** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____
Instance-no: 2 (Medical History)	
Condition (1/5)	**Intermittent atrial fibrilation**
Start date (2/5)	__/__/____ [day/month/year] or **[x] unknown**
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 3 (Medical History)

Condition (1/5)	**gouty arthritis**
Start date (2/5)	__/__/____ [day/month/year] or **[x] unknown**
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____

Instance-no: 4 (Medical History)

Condition (1/5)	**Renal anaemia**
Start date (2/5)	**21/03/2016** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 5 (Medical History)

Condition (1/5)	**Deep vein thrombosis**
Start date (2/5)	__/__/____ [day/month/year] or **[x] unknown**
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____

Instance-no: 6 (Medical History)

Condition (1/5)	**Vitamin D deficiency**
Start date (2/5)	__/__/____ [day/month/year] or **[x] unknown**
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 7 (Medical History)

Condition (1/5)	**Prostetic hyperplasia**
Start date (2/5)	**03/03/2016** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	**Urethral catheder**

Instance-no: 8 (Medical History)

Condition (1/5)	**Chronic kidney disease**
Start date (2/5)	**27/12/2013** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	**G5 D Interstitial nephritis**

Instance-no: 9 (Medical History)

Condition (1/5)	**Arthritis**
Start date (2/5)	__/__/____ [day/month/year] or **[x] unknown**
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 10 (Medical History)

Condition (1/5)	**Insomnia**
Start date (2/5)	__/__/____ [day/month/year] or **[x] unknown**
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**

Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 11 (Medical History)

Condition (1/5)	**Calciphylaxis**
Start date (2/5)	**14**/**04**/**2016** [day/month/year] or [ ] unknown
End date (3/5)	**26**/**07**/**2016** [day/month/year] or _____
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 12 (Medical History)

Condition (1/5)	**Interstitial Nephritis**
Start date (2/5)	**27**/**12**/**2013** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 13 (Medical History)

Condition (1/5)	_____
Start date (2/5)	__/__/____ [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or _____
Treated with medications at study start (4/5)	___
Comments (5/5)	_____ _____ _____

Concomitant medication [CRF-page 15/17] - Table

Instance-no: 1 (Concomitant Medication)

Medication (Trade name) (1/8)	**Concor Cor**
Start date (2/8)	**16**/**03**/**2016** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **2,5 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Intermittent atrial fibrilation** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 2 (Concomitant Medication)

Medication (Trade name) (1/8)	**Detrusitol**
Start date (2/8)	**11**/**03**/**2016** [day/month/year]
End date (3/8)	**13**/**05**/**2016** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **2 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Prostetic hyperplasia** or Adverse event: _____ or

	Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 3 (Concomitant Medication)

Medication (Trade name) (1/8)	**Dibondrin**
Start date (2/8)	**09/04/2016** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **1 dragee** frequency: **as needed**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Chronic kidney disease** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 4 (Concomitant Medication)

Medication (Trade name) (1/8)	**Novalgin**
Start date (2/8)	**09/04/2016** [day/month/year]
End date (3/8)	**14/05/2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **30 drops** frequency: **as needed**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 5 (Concomitant Medication)

Medication (Trade name) (1/8)	**Oleovit D3**
Start date (2/8)	**09/03/2016** [day/month/year]
End date (3/8)	**19/04/2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **20 drops** frequency: **once a week**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Vitamin D deficiency** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 6 (Concomitant Medication)

Medication (Trade name) (1/8)	**Temesta**
Start date (2/8)	**11/03/2016** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **1 mg** frequency: **daily**

Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Insomnia** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 7 (Concomitant Medication)

Medication (Trade name) (1/8)	**Transtec Pflaster**
Start date (2/8)	**11/03/2016** [day/month/year]
End date (3/8)	**19/04/2016** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **17,5 mcg** frequency: **every three days**
Route of administration (5/8)	**percutan**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 8 (Concomitant Medication)

Medication (Trade name) (1/8)	**Vitamin K2**
Start date (2/8)	**03/04/2016** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **45 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 9 (Concomitant Medication)

Medication (Trade name) (1/8)	**Fraxiparin**
Start date (2/8)	**09/03/2016** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **3800 IE** frequency: **five times per week**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: _____ or Adverse event: _____ or Other: **Haemodialysis (start date 09.03.2016)**
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 10 (Concomitant Medication)

Medication (Trade name) (1/8)	**Clavamox**
Start date (2/8)	**10/05/2016** [day/month/year]
End date (3/8)	**20/05/2016** [day/month/year] or _____

Dose and frequency (4/8)	total daily dose and unit: **1 G** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **Otitis media right** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 11 (Concomitant Medication)

Medication (Trade name) (1/8)	**Coldan nose droplets**
Start date (2/8)	**10**/**05**/**2016** [day/month/year]
End date (3/8)	**20**/**05**/**2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **2 drops** frequency: **daily**
Route of administration (5/8)	**nasal**
Indication (6/8)	Medical history: _____ or Adverse event: **Otitis media right** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 12 (Concomitant Medication)

Medication (Trade name) (1/8)	**Transtec Pflaster**
Start date (2/8)	**19**/**04**/**2016** [day/month/year]
End date (3/8)	**17**/**05**/**2016** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **35 mcg** frequency: **every three days**
Route of administration (5/8)	**percutan**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 13 (Concomitant Medication)

Medication (Trade name) (1/8)	**Detrusitol**
Start date (2/8)	**14**/**05**/**2016** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **1 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Prostetic hyperplasia** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 14 (Concomitant Medication)

Medication (Trade name) (1/8)	**Paracetamol**
Start date (2/8)	**16**/**04**/**2016** [day/month/year]

End date (3/8)	**16**/**04**/**2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **1000 mg** frequency: **once**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 15 (Concomitant Medication)

Medication (Trade name) (1/8)	**Novalgin**
Start date (2/8)	**16**/**04**/**2016** [day/month/year]
End date (3/8)	**16**/**04**/**2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **2,5 g** frequency: **once**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 16 (Concomitant Medication)

Medication (Trade name) (1/8)	**Novalgin**
Start date (2/8)	**23**/**04**/**2016** [day/month/year]
End date (3/8)	**23**/**04**/**2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **2,5 g** frequency: **once**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 17 (Concomitant Medication)

Medication (Trade name) (1/8)	**Kytril**
Start date (2/8)	**30**/**04**/**2016** [day/month/year]
End date (3/8)	**30**/**04**/**2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **3 mg** frequency: **once**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: _____ or Adverse event: **Nausea** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 18 (Concomitant Medication)

Medication (Trade name) (1/8)	**Kytril**
Start date (2/8)	**14/05/2016** [day/month/year]
End date (3/8)	**14/05/2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **3 mg** frequency: **once**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: _____ or Adverse event: **Emesis** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 19 (Concomitant Medication)

Medication (Trade name) (1/8)	**Paspertin**
Start date (2/8)	**16/06/2016** [day/month/year]
End date (3/8)	**16/06/2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **10 mg** frequency: **once**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: _____ or Adverse event: **Emesis** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 20 (Concomitant Medication)

Medication (Trade name) (1/8)	**Transtec Pflaster**
Start date (2/8)	**17/05/2016** [day/month/year]
End date (3/8)	**14/06/2016** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **17,5** frequency: **every three days**
Route of administration (5/8)	**percutan**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 21 (Concomitant Medication)

Medication (Trade name) (1/8)	**Transtec Pflaster**
Start date (2/8)	**14/06/2016** [day/month/year]
End date (3/8)	**16/06/2016** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **35 mcg** frequency: **every three days**
Route of administration (5/8)	**percutan**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 22 (Concomitant Medication)

Medication (Trade name) (1/8)	**Transtec Pflaster**
Start date (2/8)	**16**/**06**/**2016** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **17,5 mcg** frequency: **every three days**
Route of administration (5/8)	**percutan**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 23 (Concomitant Medication)

Medication (Trade name) (1/8)	**Kefzol**
Start date (2/8)	**23**/**04**/**2016** [day/month/year]
End date (3/8)	**23**/**04**/**2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **1 g** frequency: **once**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: _____ or Adverse event: **SAE: Fracture of femural neck** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 24 (Concomitant Medication)

Medication (Trade name) (1/8)	**Lovenox**
Start date (2/8)	**22**/**04**/**2016** [day/month/year]
End date (3/8)	**02**/**05**/**2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **20 mg** frequency: **daily**
Route of administration (5/8)	**subcutaneous**
Indication (6/8)	Medical history: _____ or Adverse event: **SAE: Fracture of femural neck** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 25 (Concomitant Medication)

Medication (Trade name) (1/8)	**Hydal**
Start date (2/8)	**22**/**04**/**2016** [day/month/year]
End date (3/8)	**24**/**04**/**2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **1 mg** frequency: **as needed**
Route of administration (5/8)	**subcutaneous**
Indication (6/8)	Medical history: _____ or Adverse event: **SAE: Fracture of femural neck** or Other: _____
Was the medication administered to treat	**no**

pain (7/8)	
Comments (8/8)	_____ _____ _____

Instance-no: 26 (Concomitant Medication)

Medication (Trade name) (1/8)	**Haldol**
Start date (2/8)	**23**/**04**/**2016** [day/month/year]
End date (3/8)	**23**/**04**/**2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **8 drops** frequency: **as needed**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **SAE: Fracture of femural neck** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 27 (Concomitant Medication)

Medication (Trade name) (1/8)	**Kytril**
Start date (2/8)	**03**/**05**/**2016** [day/month/year]
End date (3/8)	**03**/**05**/**2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **3 mg** frequency: **once**
Route of administration (5/8)	**i.v.**
Indication (6/8)	Medical history: _____ or Adverse event: **Emesis** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 28 (Concomitant Medication)

Medication (Trade name) (1/8)	_____
Start date (2/8)	__/__/____ [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: _____ frequency: _____
Route of administration (5/8)	_____
Indication (6/8)	Medical history: _____ or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	___
Comments (8/8)	_____ _____ _____

Adverse event [CRF-page 16/17] - Table

Instance-no: 1 (Adverse Event)

Adverse event (1/9)	**Fracture of femural neck**
Start date (2/9)	**22**/**04**/20**16** [day/month/year]
Severity (3/9)	**severe**

Causal relationship to study treatment (4/9)	**not related**
Serious adverse event (5/9)	**yes** if yes - please check all that apply: [ ] death [ ] life-threatening **[x] inpatient hospitalization or prolongation of existing hospitalization** [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	[ ] None [ ] Drug treatment **[x] Other** if other - please specify: **surgery**
Outcome (8/9)	**Recovered/resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **03**/**05**/20**16** [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 2 (Adverse Event)

Adverse event (1/9)	**Otitis media right**
Start date (2/9)	**10**/**05**/20**16** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**not related**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	[ ] None **[x] Drug treatment** [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Recovered/resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **20**/**05**/20**16** [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 3 (Adverse Event)

Adverse event (1/9)	**Nausea**
Start date (2/9)	**28**/**04**/20**16** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**probable**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**

Countermeasures (7/9)	[ ] None **[x] Drug treatment** [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Recovered/resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **03**/**05**/20**16** [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 4 (Adverse Event)

Adverse event (1/9)	**Emesis**
Start date (2/9)	__/**05**/20**16** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**probable**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	[ ] None **[x] Drug treatment** [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Recovered/resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **14**/**05**/20**16** [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 5 (Adverse Event)

Adverse event (1/9)	**Emesis**
Start date (2/9)	__/**05**/20**16** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**probable**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	**[x] None** [ ] Drug treatment [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Recovered/resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **02**/**06**/20**16** [day/month/year]

Comments (9/9)	_____ _____ _____

Instance-no: 6 (Adverse Event)

Adverse event (1/9)	**Emesis**
Start date (2/9)	**16**/**06**/20**16** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**probable**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	[ ] None **[x] Drug treatment** [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Recovered/resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **16**/**06**/20**16** [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 7 (Adverse Event)

Adverse event (1/9)	**Weight reduction**
Start date (2/9)	**14**/**06**/20**16** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**not related**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	**[x] None** [ ] Drug treatment [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**unknown** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: __/__/20__ [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 8 (Adverse Event)

Adverse event (1/9)	**Hematoma periorbital left site**
Start date (2/9)	**14**/**06**/20**16** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment	**not related**

(4/9)	
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	**[x] None** [ ] Drug treatment [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**unknown** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: __/__/20__ [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 9 (Adverse Event)

Adverse event (1/9)	_____
Start date (2/9)	__/__/20__ [day/month/year]
Severity (3/9)	_____
Causal relationship to study treatment (4/9)	_____
Serious adverse event (5/9)	___ if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	_____
Countermeasures (7/9)	[ ] None [ ] Drug treatment [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	_____ if recovered/resolved or recovered/resolved with sequelae - please provide stop date: __/__/20__ [day/month/year]
Comments (9/9)	_____ _____ _____

Concomitant procedure/measure [CRF-page 17/17] - Table

Instance-no: 1 (Concomitant Procedure/Measure)

Procedure (1/5)	**Haemodialysis**
Start date (2/5)	**09/03/2016** [day/month/year]
End date (3/5)	**13/04/2016** [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: **Chronic kidney disease** or Adverse event: _____ or Other: _____
Comments (5/5)	_____ _____ _____

Instance-no: 2 (Concomitant Procedure/Measure)

Procedure (1/5)	**Citrate Dialysis**
Start date (2/5)	**14/04/2016** [day/month/year]
End date (3/5)	**14/04/2016** [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: **Chronic kidney disease** or Adverse event: _____ or Other: _____
Comments (5/5)	**Skin biopsies**

Instance-no: 3 (Concomitant Procedure/Measure)

Procedure (1/5)	**Haemodialysis**
Start date (2/5)	**15/04/2016** [day/month/year]
End date (3/5)	**22/04/2016** [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: **Chronic kidney disease** or Adverse event: _____ or Other: _____
Comments (5/5)	_____ _____ _____

Instance-no: 4 (Concomitant Procedure/Measure)

Procedure (1/5)	**Citrate Dialysis**
Start date (2/5)	**23/04/2016** [day/month/year]
End date (3/5)	**30/04/2016** [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: _____ or Adverse event: **SAE: Fracture of femural neck** or Other: _____
Comments (5/5)	_____ _____ _____

Instance-no: 5 (Concomitant Procedure/Measure)

Procedure (1/5)	**Haemodialysis**
Start date (2/5)	**01/05/2016** [day/month/year]
End date (3/5)	**25/06/2016** [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: **Chronic kidney disease** or Adverse event: _____ or Other: _____
Comments (5/5)	**Patient decision to stopp haemodialysis**

Instance-no: 6 (Concomitant Procedure/Measure)

Procedure (1/5)	**Urethral catheterization (Urethral catheder)**
Start date (2/5)	**03/03/2016** [day/month/year]
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Indication (4/5)	Medical history/concomitant disease: **Prostetic hyperplasia** or Adverse event: _____ or Other: _____
Comments (5/5)	**no comments**

Instance-no: 7 (Concomitant Procedure/Measure)

Procedure (1/5)	**Joint surgery**
Start date (2/5)	**23/04/2016** [day/month/year]
End date (3/5)	**23/04/2016** [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: _____ or Adverse event: **SAE: Fracture of femural neck** or Other: _____
Comments (5/5)	**no comment**

Instance-no: 8 (Concomitant Procedure/Measure)

Procedure (1/5)	_____
Start date (2/5)	__/__/____ [day/month/year]
End date (3/5)	__/__/____ [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: _____ or Adverse event: _____ or Other: _____

Comments (5/5)	_____ _____ _____

I confirm that I have carefully examined all entries of this patient. All information entered by myself or my colleagues is, to the best of my knowledge, correct as of the date below

Date: _____

Signature and stamp of investigator: _____

Study STS-CSM-1/13, Center: Academic Teaching Hospital Feldkirch [0102]
Patient No. 2: CRF Hardcopy, 18.09.2018 , 12:58:01

Screening/Start of run-in phase [10.06.2016]

Demographic information [CRF-page 1/17]	
Date of written informed consent (1/5)	**10**/**06**/20**16** [day/month/year]
Patient ID (2/5)	**01**-**02**-**002** (country-site-patient)
Patient year of birth (3/5)	19**44** [year] Age (at date of informed consent): **72** years
Gender (4/5)	**female**
Race of patient (5/5)	**white** if other - please specify: _____ _____ _____

Inclusion/exclusion criteria [CRF-page 2/17]	
Inclusion criteria	
Patient ⩾ 18 years (1/11)	**yes**
Male or female HD patients with a diagnosis of calciphylaxis (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching) (2/11)	**yes**
Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study (3/11)	**yes**
Exclusion criteria	
Sodium metabisulfite hypersensitivity, among others the history of bronchial asthma due to known sodium metabisulfite hypersensitivity (4/11)	**no**
Pregnant or lactating patients. As pregnancy is an extremely rare event in HD patients, a pregnancy test will only be performed in ambiguous cases. (5/11)	**no**
Patients who have participated in any other investigational studies within 30 days previous to enrollment (6/11)	**no**
History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment (7/11)	**no**
Good response to conventional treatment (8/11)	**no**
Life expectancy less than 4 months in the judgement of the investigator (9/11)	**no**
Comments (10/11)	_____ _____ _____

Clinical examination [CRF-page 3/17]	
Vital signs	
Date of assessment (1/24)	**13**/**06**/20**16** [day/month/year]
Body height (2/24)	**156** cm
Body weight (3/24)	**60.1** kg
Blood pressure (measured after patient has rested for 5 minutes) (4/24)	**129** mmHg / **87** mmHg [systolic/diastolic]
Heart rate (measured after patient has rested for 5 minutes) (5/24)	**93** b/min
BMI (calculated) (6/24)	**24.7** kg/m²
12-lead ECG	
	Date: **13**/**06**/20**16** [day/month/year] Result: **abnormal, not clinically relevant**

ECG findings (7/24)	if abnormal and clinically relevant - please specify: _____ _____ _____
Physical examination	
Were physical examinations performed (8/24)	**yes** if yes - date: **13**/**06**/20**16** [day/month/year]
Head (9/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (10/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (11/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Dermatological (12/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Musculosceletal (13/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (14/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (15/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
	normal if abnormal - please specify: _____ _____

Neurological (16/24)	_____ if abnormal - clinically relevant: ___
Other (17/24)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Calciphylaxis diagnosis	
Calciphylaxis diagnosed according to typical signs and symptoms (18/24)	**yes** if yes - please check all that apply: **[x] Severe pain** **[x] Livedo** **[x] Violaceous plaques** [ ] Ulcerations **[x] Necroses** if ulcerations and/or necroses - have other causes been excluded: **yes**
Tobacco use	
Tobacco use (19/24)	**Non-smoker**
Checklist	
Does the patient have any relevant medical history or concomitant diseases (20/24)	**yes**
Does the patient receive any concomitant medication (including pain medication) (21/24)	**yes**
Any concomitant procedures/measures performed (22/24)	**yes**
Has sample for biobanking been taken (23/24)	**yes** if yes - date: **13**/**06**/20**16** [day/month/year]
Comments (24/24)	_____ _____ _____

Hematology and venous blood gas analysis [CRF-page 4/17]	
Hematology	
Date of sample (1/12)	**13**/**06**/20**16** [day/month/year]
Patient's age at sampling date (2/12)	**[x] same as at informed consent** (**72** years) or ___ years
Hemoglobin (3/12)	**95 g/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
White blood cells (4/12)	**5.5 G/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min **[x] not available**
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____.____ **mmHg** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Partial pressure of oxygen venous (8/12)	**79.3 mmHg** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with:

	_____
Oxygen saturation (9/12)	**95.1 %** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Bicarbonate (10/12)	**23.8 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	**Partial pressure of Oxygen not done**

Clinical chemistry [CRF-page 5/17]	
Clinical Chemistry	
Date of sample (1/25)	**13**/**06**/20**16** [day/month/year]
Patient's age at sampling date (2/25)	**[x] same as at informed consent** (**72** years) or ___ years
IPTH (3/25)	**544 pg/ml** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Calcium (4/25)	**1.79 mmol/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Phosphate (5/25)	**1.69 mmol/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Alk. phosphatase (6/25)	**225 U/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
pH serum (7/25)	**7.41 1/1** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	**0.52 mg/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Creatinine (9/25)	**6.6 mg/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Albumin (10/25)	**3.3 g/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Sodium (11/25)	**139 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Potassium (12/25)	**5 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Chloride (13/25)	**96 mmol/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
	0.96 mmol/l

Magnesium (14/25)	if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GOT (AST) (15/25)	**21 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GPT (ALT) (16/25)	**14 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Gamma-GT (17/25)	**15 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Amylase (18/25)	**170 U/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Lipase (19/25)	**105 U/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Urea (20/25)	**118 mg/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Uric acid (21/25)	**7.1 mg/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	**8.1 ng/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
25-Hydroxy-Vitamin D (23/25)	**40 ug/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____

Wound, pain and other assessments [CRF-page 6/17]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/4)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/4)	**yes** if yes - degree of pain: **64** mm
Comments (3/4)	_____ _____ _____

End of run-in phase

Inclusion/exclusion criteria [CRF-page 7/17]	
Inclusion criteria	
Patient $\geqslant$ 18 years (1/11)	**yes**
Male or female HD patients with a diagnosis of calciphylaxis. (Patients on peritoneal dialysis or patients with the requirement for renal	**yes**

replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching). (2/11)	
Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study (3/11)	**yes**
Exclusion criteria	
Sodium metabisulfite hypersensitivity, among others the history of bronchial asthma due to known sodium metabisulfite hypersensitivity (4/11)	**no**
Pregnant or lactating patients. As pregnancy is an extremely rare event in HD patients, a pregnancy test will only be performed in ambiguous cases. (5/11)	**no**
Patients who have participated in any other investigational studies within 30 days previous to enrollment (6/11)	**no**
History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment (7/11)	**no**
Good response to conventional treatment (8/11)	**no**
Life expectancy less than 4 months in the judgement of the investigator (9/11)	**no**
Comments (10/11)	_____ _____ _____

Completion of run-in-phase [CRF-page 8/17]	
Has a skin biopsy been taken (1/7)	**yes** if yes, date:**10**/**06**/20**16** [day/month/year] if yes - calciphylaxis diagnosis confirmed by analysis: **yes**
Has the patient agreed to participate in the clinical trial and to undergo STS treatment (2/7)	**yes**
Disease status under BSC (3/7)	**rapidly progressive disease**
Have all screening/baseline assessments been performed and is patient considered eligible for treatment start (4/7)	**yes** if no - please check all that apply: [ ] patient did not meet all in-/exclusion criteria [ ] withdrawal of informed consent by the patient [ ] discretion of the investigator [ ] calciphylaxis diagnosis not confirmed [ ] other reason if other reason - please specify: _____ _____ _____
Comments (5/7)	_____ _____ _____

Visits

Visits [CRF-page 9/17] - Table	
Instance-no: 1 (Visits)	
Visit 0 Start of visit [Instance-no: 1, page 1/5]	
Actual date of visit (1/6)	**16**/**06**/20**16** [day/month/year] [ ] not done
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (2/6)	**no**
Any new concomitant procedures/measures or changes in concomitant procedures/measures (3/6)	**no**
Any new adverse events or changes in adverse	

events (4/6)	**no**
Soft tissue radiographs	
Have soft tissue radiographs been taken (optional) (5/6)	**yes** if yes, date: **13**/**06**/20**16** [day/month/year]
Comments (6/6)	**Data is correct**
Clinical examination [Instance-no: 1, page 2/5]	
Vital signs	
Date of assessment (1/17)	**16**/**06**/20**16** [day/month/year]
Body weight (2/17)	**59.9** kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	**148** mmHg / **96** mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	**71** b/min [ ] not done
BMI (calculated) (5/17)	**24.6** kg/m²
Physical examination	
Were physical examinations performed (6/17)	**yes** if yes - date: **16**/**06**/20**16** [day/month/year]
Head (7/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (8/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (9/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Dermatological (10/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Musculosceletal (11/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (12/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___

Gastrointestinal (13/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Neurological (14/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Other (15/17)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Biobanking	
Has sample for biobanking been taken (16/17)	**yes** if yes - date: **16**/**06**/20**16** [day/month/year]
Comments (17/17)	_____ _____ _____
Hematology and venous blood gas analysis [Instance-no: 1, page 3/5]	
Hematology	
Date of sample (1/12)	**16**/**06**/20**16** [day/month/year]
Patient's age at sampling date (2/12)	**[x] same as at informed consent** (**72** years) or ___ years
Hemoglobin (3/12)	**95 g/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
White blood cells (4/12)	**5.9 G/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min **[x] not available**
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____**.**____ **mmHg [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Partial pressure of oxygen venous (8/12)	**90.9 mmHg** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Oxygen saturation (9/12)	**97.4 %** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Bicarbonate (10/12)	**22.2 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
	_____

If "other" was chosen above for at least one time - please specify (11/12)	_____ _____
Comments (12/12)	_____ _____ _____
Clinical chemistry [Instance-no: 1, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	**16**/**06**/20**16** [day/month/year]
Patient's age at sampling date (2/25)	**[x] same as at informed consent** (**72** years) or ___ years
IPTH (3/25)	**747 pg/ml** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Calcium (4/25)	**1.86 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Phosphate (5/25)	**1.61 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Alk. phosphatase (6/25)	**223 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
pH serum (7/25)	**7.42 1/1** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	**0.91 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Creatinine (9/25)	**6.8 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Albumin (10/25)	**3.8 g/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Sodium (11/25)	**135 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Potassium (12/25)	**5.1 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Chloride (13/25)	**97 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Magnesium (14/25)	**0.99 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GOT (AST) (15/25)	**24 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GPT (ALT) (16/25)	**12 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with:

	_____
Gamma-GT (17/25)	**18 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Amylase (18/25)	**121 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Lipase (19/25)	**39 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Urea (20/25)	**104 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Uric acid (21/25)	**6.8 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	**8.7 ng/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
25-Hydroxy-Vitamin D (23/25)	**47 ug/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____
Wound, pain and other assessments [Instance-no: 1, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	**yes** if yes - degree of pain: **21** mm
Bone Mineral Density	
Has bone mineral density been assessed (3/6)	**yes** if yes: method:**DEXA scan** t-score:**-3.9** z-score:**-1.9**
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (4/6)	**yes** if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: **mildly ill**
Comments (5/6)	_____ _____ _____
Instance-no: 2 (Visits)	
Visit 1 Start of visit [Instance-no: 2, page 1/3]	
Planned date of visit (1/7)	14/07/2016 [day/month/year]
Actual date of visit (2/7)	**14**/**07**/20**16** [day/month/year] [ ] not done if deviation from planned date - please provide reason: _____

	_____ _____
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	**yes**
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	**no**
Any new adverse events or changes in adverse events (5/7)	**no**
Any new lesions under STS treatment (6/7)	**no**
Comments (7/7)	_____ _____ _____
Clinical examination [Instance-no: 2, page 2/3]	
Vital signs	
Date of assessment (1/16)	**14**/**07**/20**16** [day/month/year]
Body weight (2/16)	**59** kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/16)	**149** mmHg / **85** mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/16)	**73** b/min [ ] not done
BMI (calculated) (5/16)	**24.2** kg/m²
Physical examination	
Were physical examinations performed (6/16)	**yes** if yes - date: **14**/**07**/20**16** [day/month/year]
Head (7/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (8/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (9/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Dermatological (10/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Musculosceletal (11/16)	**normal** if abnormal - please specify: _____ _____ _____

	if abnormal - clinically relevant: ___
Respiratory (12/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (13/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Neurological (14/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Other (15/16)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Comments (16/16)	_____ _____ _____
Wound, pain and other assessments [Instance-no: 2, page 3/3]	
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (1/5)	**yes** if yes - degree of pain: **21** mm
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (2/5)	**yes** if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: **normal, not at all ill**
Was the clinical global impression improvement assessed using the CGI-I-score (3/5)	**yes** if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: **minimally improved**
Comments (4/5)	_____ _____ _____
Instance-no: 3 (Visits)	
Visit 2 Start of visit [Instance-no: 3, page 1/5]	
Planned date of visit (1/7)	11/08/2016 [day/month/year]
Actual date of visit (2/7)	**11**/**08**/20**16** [day/month/year] [ ] not done if deviation from planned date - please provide reason: _____ _____ _____
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain	**no**

medication) (3/7)	
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	**no**
Any new adverse events or changes in adverse events (5/7)	**no**
Any new lesions under STS treatment (6/7)	**no**
Comments (7/7)	_____ _____ _____
Clinical examination [Instance-no: 3, page 2/5]	
Vital signs	
Date of assessment (1/17)	**11**/**08**/20**16** [day/month/year]
Body weight (2/17)	**59.1** kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	**171** mmHg / **108** mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	**81** b/min [ ] not done
BMI (calculated) (5/17)	**24.3** kg/m²
Physical examination	
Were physical examinations performed (6/17)	**yes** if yes - date: **11**/**08**/20**16** [day/month/year]
Head (7/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (8/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (9/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Dermatological (10/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Musculosceletal (11/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
	normal if abnormal - please specify: _____

Respiratory (12/17)	_____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (13/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Neurological (14/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Other (15/17)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Biobanking	
Has sample for biobanking been taken (16/17)	**yes** if yes - date: **11**/**08**/20**16** [day/month/year]
Comments (17/17)	_____ _____ _____
Hematology and venous blood gas analysis [Instance-no: 3, page 3/5]	
Hematology	
Date of sample (1/12)	**11**/**08**/20**16** [day/month/year]
Patient's age at sampling date (2/12)	**[x] same as at informed consent** (**72** years) or ___ years
Hemoglobin (3/12)	**104 g/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
White blood cells (4/12)	**4.9 G/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min **[x] not available**
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____.____ **mmHg [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Partial pressure of oxygen venous (8/12)	**70.2 mmHg** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Oxygen saturation (9/12)	**93.4 %** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____

Bicarbonate (10/12)	**27.2 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	_____ _____ _____
Clinical chemistry [Instance-no: 3, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	**11**/**08**/20**16** [day/month/year]
Patient's age at sampling date (2/25)	**[x] same as at informed consent** (**72** years) or ___ years
IPTH (3/25)	**722 pg/ml** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Calcium (4/25)	**2.45 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Phosphate (5/25)	**1.27 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Alk. phosphatase (6/25)	**299 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
pH serum (7/25)	**7.43 1/1** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	**0.37 mg/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Creatinine (9/25)	**5.4 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Albumin (10/25)	**3.8 g/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Sodium (11/25)	**143 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Potassium (12/25)	**5.3 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Chloride (13/25)	**95 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Magnesium (14/25)	**1.03 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
	22 U/l [ ] not available if outside normal limits - clinically relevant ? ___

GOT (AST) (15/25)	if clinically relevant - causal relationship with: _____
GPT (ALT) (16/25)	**16 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Gamma-GT (17/25)	**22 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Amylase (18/25)	**124 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Lipase (19/25)	**28 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Urea (20/25)	**55 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Uric acid (21/25)	**4.9 mg/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	**11.5 ng/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
25-Hydroxy-Vitamin D (23/25)	**53 ug/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____
Wound, pain and other assessments [Instance-no: 3, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	**yes** if yes - degree of pain: **43** mm
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (3/6)	**yes** if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: **mildly ill**
Was the clinical global impression improvement assessed using the CGI-I-score (4/6)	**yes** if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: **minimally improved**
Comments (5/6)	_____ _____ _____
Instance-no: 4 (Visits)	
Visit 3 Start of visit [Instance-no: 4, page 1/5]	
Planned date of visit (1/7)	06/10/2016 [day/month/year]

Actual date of visit (2/7)	**07**/**10**/20**16** [day/month/year] [ ] not done if deviation from planned date - please provide reason: _____ _____ _____
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	**no**
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	**no**
Any new adverse events or changes in adverse events (5/7)	**no**
Any new lesions under STS treatment (6/7)	**no**
Comments (7/7)	_____ _____ _____
Clinical examination [Instance-no: 4, page 2/5]	
Vital signs	
Date of assessment (1/17)	**07**/**10**/20**16** [day/month/year]
Body weight (2/17)	**58.6** kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	**139** mmHg / **77** mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	**74** b/min [ ] not done
BMI (calculated) (5/17)	**24.1** kg/m²
Physical examination	
Were physical examinations performed (6/17)	**yes** if yes - date: **07**/**10**/20**16** [day/month/year]
Head (7/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (8/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (9/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Dermatological (10/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
	normal if abnormal - please specify: _____

Musculosceletal (11/17)	_____ _____ if abnormal - clinically relevant: ___
Respiratory (12/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (13/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Neurological (14/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Other (15/17)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Biobanking	
Has sample for biobanking been taken (16/17)	**yes** if yes - date: **07**/**10**/20**16** [day/month/year]
Comments (17/17)	_____ _____ _____
Hematology and venous blood gas analysis [Instance-no: 4, page 3/5]	
Hematology	
Date of sample (1/12)	**07**/**10**/20**16** [day/month/year]
Patient's age at sampling date (2/12)	**[x] same as at informed consent** (**72** years) or ___ years
Hemoglobin (3/12)	**104 g/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
White blood cells (4/12)	**4.5 G/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min **[x] not available**
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____.____ **mmHg [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____

Partial pressure of oxygen venous (8/12)	**81.2 mmHg** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Oxygen saturation (9/12)	**94 %** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Bicarbonate (10/12)	**19 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	_____ _____ _____
Clinical chemistry [Instance-no: 4, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	**07**/**10**/20**16** [day/month/year]
Patient's age at sampling date (2/25)	**[x] same as at informed consent** (**72** years) or ___ years
IPTH (3/25)	**123 pg/ml** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Calcium (4/25)	**1.99 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Phosphate (5/25)	**1.15 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Alk. phosphatase (6/25)	**346 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
pH serum (7/25)	**7.31 1/1** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	**0.64 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Creatinine (9/25)	**4.3 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Albumin (10/25)	**3.7 g/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Sodium (11/25)	**140 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Potassium (12/25)	**5.5 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
	91 mmol/l [ ] not available if outside normal limits - clinically relevant ? **no**

Chloride (13/25)	if clinically relevant - causal relationship with: _____
Magnesium (14/25)	**0.93 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GOT (AST) (15/25)	**22 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GPT (ALT) (16/25)	**13 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Gamma-GT (17/25)	**33 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Amylase (18/25)	**173 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Lipase (19/25)	**105 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Urea (20/25)	**62 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Uric acid (21/25)	**3.6 mg/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	**20.2 ng/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
25-Hydroxy-Vitamin D (23/25)	**50 ug/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____
Wound, pain and other assessments [Instance-no: 4, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	**yes** if yes - degree of pain: **0** mm
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (3/6)	**yes** if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: **normal, not at all ill**
Was the clinical global impression improvement assessed using the CGI-I-score (4/6)	**yes** if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: **very much improved since the initiation of treatment**

Comments (5/6)	_____ _____ _____

Instance-no: 5 (Visits)

Visit 4 Start of visit [Instance-no: 5, page 1/5]	
Planned date of visit (1/7)	01/12/2016 [day/month/year]
Actual date of visit (2/7)	**30**/**11**/20**16** [day/month/year] [ ] not done if deviation from planned date - please provide reason: **Data is correct.**
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	**no**
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	**no**
Any new adverse events or changes in adverse events (5/7)	**no**
Any new lesions under STS treatment (6/7)	**no**
Comments (7/7)	_____ _____ _____
Clinical examination [Instance-no: 5, page 2/5]	
Vital signs	
Date of assessment (1/17)	**30**/**11**/20**16** [day/month/year]
Body weight (2/17)	**57.4** kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	**150** mmHg / **93** mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	**72** b/min [ ] not done
BMI (calculated) (5/17)	**23.6** kg/m²
Physical examination	
Were physical examinations performed (6/17)	**yes** if yes - date: **30**/**11**/20**16** [day/month/year]
Head (7/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (8/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (9/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Dermatological (10/17)	**normal** if abnormal - please specify: _____ _____

	_____ if abnormal - clinically relevant: ___
Musculosceletal (11/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (12/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (13/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Neurological (14/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Other (15/17)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Biobanking	
Has sample for biobanking been taken (16/17)	**yes** if yes - date: **30**/**11**/20**16** [day/month/year]
Comments (17/17)	_____ _____ _____
Hematology and venous blood gas analysis [Instance-no: 5, page 3/5]	
Hematology	
Date of sample (1/12)	**30**/**11**/20**16** [day/month/year]
Patient's age at sampling date (2/12)	**[x] same as at informed consent** (**72** years) or ___ years
Hemoglobin (3/12)	**104 g/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
White blood cells (4/12)	**4.3 G/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____

T50 Test (6/12)	___ min **[x] not available**
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____._____ **mmHg [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Partial pressure of oxygen venous (8/12)	**66.9 mmHg** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Oxygen saturation (9/12)	**89.6 %** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Bicarbonate (10/12)	**21.1 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	_____ _____ _____
Clinical chemistry [Instance-no: 5, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	**30**/**11**/20**16** [day/month/year]
Patient's age at sampling date (2/25)	**[x] same as at informed consent** (**72** years) or ___ years
IPTH (3/25)	**563 pg/ml** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Calcium (4/25)	**2.22 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Phosphate (5/25)	**1.29 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Alk. phosphatase (6/25)	**332 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
pH serum (7/25)	**7.33 1/1** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	**0.25 mg/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Creatinine (9/25)	**3.9 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Albumin (10/25)	**3.8 g/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Sodium (11/25)	**139 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____

Potassium (12/25)	**5.7 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Chloride (13/25)	**89 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Magnesium (14/25)	**1 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GOT (AST) (15/25)	**15 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GPT (ALT) (16/25)	**10 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Gamma-GT (17/25)	**22 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Amylase (18/25)	**155 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Lipase (19/25)	**47 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Urea (20/25)	**58 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Uric acid (21/25)	**3.5 mg/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	**10.5 ng/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
25-Hydroxy-Vitamin D (23/25)	**46 ug/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____
Wound, pain and other assessments [Instance-no: 5, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	**yes** if yes - degree of pain: **0** mm
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (3/6)	**yes** if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time:

	normal, not at all ill
Was the clinical global impression improvement assessed using the CGI-I-score (4/6)	**yes** if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: **minimally improved**
Comments (5/6)	_____ _____ _____

Instance-no: 6 (Visits)

Visit 5 Start of visit [Instance-no: 6, page 1/3]	
Planned date of visit (1/7)	23/02/2017 [day/month/year]
Actual date of visit (2/7)	**22**/**02**/20**17** [day/month/year] [ ] not done if deviation from planned date - please provide reason: _____ _____ _____
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	**yes**
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	**no**
Any new adverse events or changes in adverse events (5/7)	**no**
Any new lesions under STS treatment (6/7)	**no**
Comments (7/7)	_____ _____ _____
Clinical examination [Instance-no: 6, page 2/3]	
Vital signs	
Date of assessment (1/16)	**22**/**02**/20**17** [day/month/year]
Body weight (2/16)	**56.3** kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/16)	**163** mmHg / **102** mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/16)	**94** b/min [ ] not done
BMI (calculated) (5/16)	**23.1** kg/m²
Physical examination	
Were physical examinations performed (6/16)	**yes** if yes - date: **22**/**02**/20**17** [day/month/year]
Head (7/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (8/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (9/16)	**normal** if abnormal - please specify: _____ _____ _____

	if abnormal - clinically relevant: ___
Dermatological (10/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Musculosceletal (11/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (12/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (13/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Neurological (14/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Other (15/16)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Comments (16/16)	_____ _____ _____
Wound, pain and other assessments [Instance-no: 6, page 3/3]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	**yes** if yes - degree of pain: **0** mm
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (3/6)	**yes** if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: **normal, not at all ill**

Was the clinical global impression improvement assessed using the CGI-I-score (4/6)	**yes** if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: **very much improved since the initiation of treatment**
Comments (5/6)	_____ _____ _____

Instance-no: 7 (Visits)

Visit 6 Start of visit [Instance-no: 7, page 1/5]	
Planned date of visit (1/7)	18/05/2017 [day/month/year]
Actual date of visit (2/7)	**17**/**05**/20**17** [day/month/year] [ ] not done if deviation from planned date - please provide reason: _____ _____ _____
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	**yes**
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	**no**
Any new adverse events or changes in adverse events (5/7)	**no**
Any new lesions under STS treatment (6/7)	**no**
Comments (7/7)	_____ _____ _____
Clinical examination [Instance-no: 7, page 2/5] Vital signs	
Date of assessment (1/17)	**17**/**05**/20**17** [day/month/year]
Body weight (2/17)	**55.8** kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	**149** mmHg / **73** mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	**92** b/min [ ] not done
BMI (calculated) (5/17)	**22.9** kg/m²
Physical examination	
Were physical examinations performed (6/17)	**yes** if yes - date: **17**/**05**/20**17** [day/month/year]
Head (7/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (8/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (9/17)	**normal** if abnormal - please specify: _____ _____ _____

	if abnormal - clinically relevant: ___
Dermatological (10/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Musculosceletal (11/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (12/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (13/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Neurological (14/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Other (15/17)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Biobanking	
Has sample for biobanking been taken (16/17)	**yes** if yes - date: **17**/**05**/20**17** [day/month/year]
Comments (17/17)	_____ _____ _____
Hematology and venous blood gas analysis [Instance-no: 7, page 3/5]	
Hematology	
Date of sample (1/12)	**17**/**05**/20**17** [day/month/year]
Patient's age at sampling date (2/12)	[ ] same as at informed consent (**72** years) or **73** years
Hemoglobin (3/12)	**98 g/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
	4.6 G/l [ ] not available

White blood cells (4/12)	if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min **[x] not available**
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____.____ **mmHg [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Partial pressure of oxygen venous (8/12)	**63.4 mmHg** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Oxygen saturation (9/12)	**91.6 %** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Bicarbonate (10/12)	**25.6 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	_____ _____ _____
Clinical chemistry [Instance-no: 7, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	**17**/**05**/20**17** [day/month/year]
Patient's age at sampling date (2/25)	[ ] same as at informed consent (**72** years) or **73** years
IPTH (3/25)	**271 pg/ml** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Calcium (4/25)	**1.83 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Phosphate (5/25)	**1.12 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Alk. phosphatase (6/25)	**160 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
pH serum (7/25)	**7.41 1/1** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	**0.93 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Creatinine (9/25)	**4.7 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
	3.4 g/dl [ ] not available

Albumin (10/25)	if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Sodium (11/25)	**141 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Potassium (12/25)	**5.4 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Chloride (13/25)	**97 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Magnesium (14/25)	**0.96 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GOT (AST) (15/25)	**20 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GPT (ALT) (16/25)	**12 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Gamma-GT (17/25)	**17 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Amylase (18/25)	**102 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Lipase (19/25)	**30 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Urea (20/25)	**55 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Uric acid (21/25)	**5.1 mg/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	**9.4 ng/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
25-Hydroxy-Vitamin D (23/25)	**54 ug/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____
Wound, pain and other assessments [Instance-no: 7, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/7)	**no**

VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/7)	**yes** if yes - degree of pain: **0** mm
Bone Mineral Density	
Has bone mineral density been assessed (3/7)	**yes** if yes: method:**DEXA scan** t-score:**-3.7** z-score:**-1.7**
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (4/7)	**yes** if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: **normal, not at all ill**
Was the clinical global impression improvement assessed using the CGI-I-score (5/7)	**yes** if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: **much improved**
Comments (6/7)	_____ _____ _____

Study medication

Study medication [CRF-page 10/17] - Table	
Instance-no: 1 (Study Medication)	
Dosage (1/5)	**25** g **3** times a week
Dosage start date (2/5)	**16**/**06**/20**16** [day/month/year]
Dosage stop date (3/5)	**28**/**11**/20**16** [day/month/year] or [ ] currently ongoing
Number of administrations with this dosage (4/5)	**72**
Comments (5/5)	**According to the protocol the dose of 25g should be administered 30min before end of dialyses. However the Infusion start time differs between 60min before end of dialysis to few min after end of dialysis on some administration dates.**
Instance-no: 2 (Study Medication)	
Dosage (1/6)	___.__ g _ times a week
Dosage start date (2/6)	__/__/20__ [day/month/year]
Dosage stop date (3/6)	__/__/20__ [day/month/year] or [ ] currently ongoing
Number of administrations with this dosage (4/6)	___
Reason for dosage change (5/6)	_____ _____ _____
Comments (6/6)	_____ _____ _____

Lesions

Lesions [CRF-page 11/17] - Table	
Instance-no: 1 (Lesions)	
Lesion (1/25)	Lesion number: **1** Lesion location: **right lateral calf**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	**30**/**11**/20**16** [day/month/year] or [ ] still present
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **13**/**06**/20**16** [day/month/year] or _____
	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **2** cm^2 or [ ] Wound area not assessed Size:

Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	**2** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **0** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **3** Total score: **21**
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **2.514** cm^2 or [ ] Wound area not assessed Size: **2** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **1** Total amount of granulation tissue: **3** Edges: **2** Periulcer skin viability: **0** Total score: **18**
Photodocumentation V0 (7/25)	Date: **16**/**06**/20**16** [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **2.2** cm^2 or [ ] Wound area not assessed Size: **2** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **0** Total amount of granulation tissue: **4** Edges: **1** Periulcer skin viability: **3** Total score: **20**
	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **2.693** cm^2 or [ ] Wound area not assessed Size: **2** Depth: **2**

Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Necrotic tissue type: **1** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **0** Total score: **19**
Photodocumentation V2 (10/25)	Date: **11**/**08**/20**16** [day/month/year] or _____
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0.15** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **3** Total score: **3**
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **1** Total score: **1**
Photodocumentation V3 (13/25)	Date: **07**/**10**/20**16** [day/month/year] or _____
	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0.11** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type:

Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	**0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **3** Total score: **3**
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **0.229** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **1** Total score: **1**
Photodocumentation V4 (16/25)	Date: **30**/**11**/20**16** [day/month/year] or _____
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0.07** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **3** Total score: **3**
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **0.09** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0**

	Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **2** Total score: **2**
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _

	Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	_____ _____ _____
Instance-no: 2 (Lesions)	
Lesion (1/25)	Lesion number: **2** Lesion location: **right claf ventral**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	**11**/**08**/20**16** [day/month/year] or [ ] still present
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **13**/**06**/20**16** [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0.16** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **3** Total score: **3**
	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **0.18** cm^2 or [ ] Wound area not assessed Size: **0**

Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **2** Total score: **2**
Photodocumentation V0 (7/25)	Date: **16**/**06**/20**16** [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0.26** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **3** Total score: **3**
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **1** Total score: **1**
Photodocumentation V2 (10/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth:

Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	_ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _

Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue:

Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	_ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue:

	_ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	_____ _____ _____

Instance-no: 3 (Lesions)

Lesion (1/25)	Lesion number: **3** Lesion location: **right calf ventral below knee**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	**11**/**08**/20**16** [day/month/year] or [ ] still present
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **13**/**06**/20**16** [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0.17** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **3** Total score: **3**
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **0.05** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **2** Total score: **2**
Photodocumentation V0 (7/25)	Date: **16**/**06**/20**16** [day/month/year] or _____
	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size:

Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	**0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **3** Total score: **3**
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **2** Total score: **2**
Photodocumentation V2 (10/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _

Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type:

Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	_ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _

	Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	_____ _____ _____
Instance-no: 4 (Lesions)	
Lesion (1/25)	Lesion number: **4** Lesion location: **right first toe medial MCP-joint**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	**30**/**11**/20**16** [day/month/year] or [ ] still present
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **13**/**06**/20**16** [day/month/year] or _____
	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0.5** cm^2 or [ ] Wound area not assessed

Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Size: **1** Depth: **1** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **1** Total amount of granulation tissue: **1** Edges: **1** Periulcer skin viability: **3** Total score: **8**
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **0.07** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **0** Total score: **0**
Photodocumentation V0 (7/25)	Date: **16**/**06**/20**16** [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **1.99** cm^2 or [ ] Wound area not assessed Size: **1** Depth: **2** Necrotic tissue type: **1** Total amount of necrotic tissue: **1** Granulation tissue type: **1** Total amount of granulation tissue: **1** Edges: **1** Periulcer skin viability: **2** Total score: **10**
	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **0.415** cm^2 or [ ] Wound area not assessed Size: **0**

Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **0** Total score: **0**
Photodocumentation V2 (10/25)	Date: **11**/**08**/20**16** [day/month/year] or _____
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0.43** cm^2 or [ ] Wound area not assessed Size: **1** Depth: **1** Necrotic tissue type: **1** Total amount of necrotic tissue: **1** Granulation tissue type: **1** Total amount of granulation tissue: **1** Edges: **2** Periulcer skin viability: **3** Total score: **11**
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **1.865** cm^2 or [ ] Wound area not assessed Size: **1** Depth: **1** Necrotic tissue type: **1** Total amount of necrotic tissue: **1** Granulation tissue type: **1** Total amount of granulation tissue: **2** Edges: **1** Periulcer skin viability: **1** Total score: **9**
Photodocumentation V3 (13/25)	Date: **07**/**10**/20**16** [day/month/year] or _____
	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0.22** cm^2 or [ ] Wound area not assessed Size: **0** Depth:

Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	**0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **3** Total score: **3**
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___**.**__ cm^2 or **[x] Wound area not assessed** Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **1** Total score: **1**
Photodocumentation V4 (16/25)	Date: **30**/**11**/20**16** [day/month/year] or _____
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0.17** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **3** Total score: **3**
	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___**.**__ cm^2 or **[x] Wound area not assessed** Size: **0** Depth: **0** Necrotic tissue type: **0**

Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **0** Total score: **0**
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **not applicable (lesion not present at date of visit)**
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V6	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _

(Dermatologist 1) (23/25)	Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	_____ _____ _____
Instance-no: 5 (Lesions)	
Lesion (1/25)	Lesion number: __ Lesion location: _____
Date of occurrence (2/25)	__/__/20__ [day/month/year] or [ ] before study start
Date of healing (3/25)	__/__/20__ [day/month/year] or [ ] still present
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size:

Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	_ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V0 (7/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V2 (10/25)	Date: __/__/20__ [day/month/year] or _____
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _

Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type:

Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	_ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or _____
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _

Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type:

	_ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	_____ _____ _____

Follow-up telephone interviews

Follow-up telephone interviews [CRF-page 12/17] - Table	
Instance-no: 1 (Follow-up telephone interviews)	
Follow-up telephone interview 1 Patient status [Instance-no: 1, page 1/1]	
Date of telephone call (1/7)	**15**/**09**/20**17** [day/month/year]
Survival status	
Patient alive (2/7)	**no**
Disease status	
Is the disease still present (3/7)	___
Continuation STS-treatment	
Has the patient received further STS-treatment since last visit (4/7)	**yes**
Further treatment	
Any further or additional treatment (5/7)	**no**
New calciphylaxis medication	
Any new medication for treatment of calciphylaxis (6/7)	**no**
Comments (7/7)	**Follow up contact early performed due to notification of patient death. last study treatment on 28.11.16 - 10 month after last IMP.**
Instance-no: 2 (Follow-up telephone interviews)	
Follow-up telephone interview 2 Patient status [Instance-no: 2, page 1/1]	
Date of telephone call (1/7)	__/__/20__ [day/month/year]
Survival status	
Patient alive (2/7)	___
Disease status	
Is the disease still present (3/7)	___
Continuation STS-treatment	
Has the patient received further STS-treatment since last visit (4/7)	___
Further treatment	
Any further or additional treatment (5/7)	___
New calciphylaxis medication	
Any new medication for treatment of calciphylaxis (6/7)	___
Comments (7/7)	_____ _____ _____

End of study [15.09.2017]

End of study [CRF-page 13/17]	
Date of study end (1/6)	**15**/**09**/20**17** [day/month/year]
Has the patient been listed on a transplant waiting list (2/6)	**no** if yes, date: __/__/20__ [day/month/year]
Date of last contact when patient was alive (3/6)	**15**/**09**/20**17** [day/month/year]

Reason of study end (4/6)	**death** if early discontinuation, lost to follow-up or other - please specify: _____ _____ _____ if patient died - date of death: **15**/**09**/20**17** [day/month/year] [ ] not available reason of death: **other** if other reason - please specify: **cerebral bleeding**
Has all patient data been entered as far as possible and checked, all data can be set read-only (5/6)	**yes**
Comments (6/6)	_____ _____ _____

Medical history, concomitant medication and procedures, adverse events

Medical history [CRF-page 14/17] - Table

Instance-no: 1 (Medical History)

Condition (1/5)	**chronic kidney disease**
Start date (2/5)	**22**/**01**/**2010** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 2 (Medical History)

Condition (1/5)	**Calciphylaxis**
Start date (2/5)	**14**/**04**/**2016** [day/month/year] or [ ] unknown
End date (3/5)	**30**/**11**/**2016** [day/month/year] or _____
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 3 (Medical History)

Condition (1/5)	**Hyperparathyreoidism**
Start date (2/5)	**23**/**06**/**2010** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 4 (Medical History)

Condition (1/5)	**Atrial fibrilation**
Start date (2/5)	**13**/**06**/**2010** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 5 (Medical History)

Condition (1/5)	**Renal anaemia**
Start date (2/5)	**23**/**06**/**2010** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**

Comments (5/5)	_____ _____ _____

Instance-no: 6 (Medical History)

Condition (1/5)	**Renal Hypertension**
Start date (2/5)	**22/01/2010** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____

Instance-no: 7 (Medical History)

Condition (1/5)	**Hypercholesterinaemia**
Start date (2/5)	**22/01/2010** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____

Instance-no: 8 (Medical History)

Condition (1/5)	**Fundus Hypertonicus**
Start date (2/5)	**13/03/1998** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____

Instance-no: 9 (Medical History)

Condition (1/5)	**Hypertensiv heart disease**
Start date (2/5)	**22/01/2010** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____

Instance-no: 10 (Medical History)

Condition (1/5)	**Hyperurikaemia**
Start date (2/5)	**22/01/2010** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____

Instance-no: 11 (Medical History)

Condition (1/5)	**Distal renal tubular azidosis**
Start date (2/5)	**30/01/2013** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____

Instance-no: 12 (Medical History)

Condition (1/5)	**HIT Typ II (Heparin induced thrombopenia typ II)**
Start date (2/5)	**16/09/2014** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
	_____

Comments (5/5)	_____ _____

Instance-no: 13 (Medical History)

Condition (1/5)	**Depression**
Start date (2/5)	__/__/____ [day/month/year] or **[x] unknown**
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 14 (Medical History)

Condition (1/5)	_____
Start date (2/5)	__/__/____ [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or _____
Treated with medications at study start (4/5)	___
Comments (5/5)	_____ _____ _____

Concomitant medication [CRF-page 15/17] - Table

Instance-no: 1 (Concomitant Medication)

Medication (Trade name) (1/8)	**Atarax**
Start date (2/8)	**28/01/2015** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **25 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **chronic kidney disease** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 2 (Concomitant Medication)

Medication (Trade name) (1/8)	**Bisoprolol**
Start date (2/8)	**31/07/2015** [day/month/year]
End date (3/8)	**21/02/2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **2.5 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Atrial fibrilation** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 3 (Concomitant Medication)

Medication (Trade name) (1/8)	**Citalopram**
Start date (2/8)	**09/09/2015** [day/month/year]
End date (3/8)	**21/02/2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **10 mg** frequency: **daily**

Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Depression** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 4 (Concomitant Medication)

Medication (Trade name) (1/8)	**Lasix**
Start date (2/8)	**31/07/2015** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **500 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **chronic kidney disease** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 5 (Concomitant Medication)

Medication (Trade name) (1/8)	**Mexalen**
Start date (2/8)	**10/06/2016** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **500 mg** frequency: **as needed**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 6 (Concomitant Medication)

Medication (Trade name) (1/8)	**Mimpara**
Start date (2/8)	**10/06/2016** [day/month/year]
End date (3/8)	**31/08/2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **30 mg** frequency: **Three times per week**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hyperparathyreoidism** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 7 (Concomitant Medication)

Medication (Trade name) (1/8)	**Mimpara**
Start date (2/8)	**10/06/2016** [day/month/year]
End date (3/8)	**31/08/2016** [day/month/year] or **dosage changed**

Dose and frequency (4/8)	total daily dose and unit: **60 mg** frequency: **four times per week**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hyperparathyreoidism** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 8 (Concomitant Medication)

Medication (Trade name) (1/8)	**Pantoloc**
Start date (2/8)	**07/11/2014** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **40 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: _____ or Other: **Prophylaxis of peptic ulcera**
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 9 (Concomitant Medication)

Medication (Trade name) (1/8)	**Renvela**
Start date (2/8)	**23/01/2015** [day/month/year]
End date (3/8)	**02/07/2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **2400 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **chronic kidney disease** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 10 (Concomitant Medication)

Medication (Trade name) (1/8)	**Vitamin K2**
Start date (2/8)	**10/06/2016** [day/month/year]
End date (3/8)	**02/07/2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **45 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 11 (Concomitant Medication)

Medication (Trade name) (1/8)	**Aranesp**

Start date (2/8)	**10/06/2016** [day/month/year]
End date (3/8)	**22/06/2016** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **30 mcg** frequency: **three times per week**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: **Renal anaemia** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 12 (Concomitant Medication)

Medication (Trade name) (1/8)	**Arixtra**
Start date (2/8)	**05/08/2015** [day/month/year]
End date (3/8)	**16/06/2016** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **1.5 mg** frequency: **Three times per week**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: **chronic kidney disease** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 13 (Concomitant Medication)

Medication (Trade name) (1/8)	**Ferrlecit**
Start date (2/8)	**13/06/2016** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **62.5 mg** frequency: **once per week**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: **Renal anaemia** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 14 (Concomitant Medication)

Medication (Trade name) (1/8)	**Folsan**
Start date (2/8)	**17/06/2016** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **5 mg** frequency: **every two weeks after dialysis**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Renal anaemia** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 15 (Concomitant Medication)

Medication (Trade name) (1/8)	**Fenistil ret**

Start date (2/8)	**02**/**07**/**2016** [day/month/year]
End date (3/8)	**25**/**01**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **4 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **chronic kidney disease** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 16 (Concomitant Medication)

Medication (Trade name) (1/8)	**Paspertin**
Start date (2/8)	**21**/**06**/**2016** [day/month/year]
End date (3/8)	**23**/**08**/**2016** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **10 mg** frequency: **six times per week**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: _____ or Adverse event: **Nausea during STS-administration** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 17 (Concomitant Medication)

Medication (Trade name) (1/8)	**Sevelamercarbonat**
Start date (2/8)	**02**/**07**/**2016** [day/month/year]
End date (3/8)	**05**/**05**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **2400 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **chronic kidney disease** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 18 (Concomitant Medication)

Medication (Trade name) (1/8)	**Mimpara**
Start date (2/8)	**07**/**02**/**2017** [day/month/year]
End date (3/8)	**10**/**05**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **60 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hyperparathyreoidism** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____

	_____

Instance-no: 19 (Concomitant Medication)

Medication (Trade name) (1/8)	**Amlodipin**
Start date (2/8)	**09/09/2016** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **5 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Renal Hypertension** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 20 (Concomitant Medication)

Medication (Trade name) (1/8)	**Aranesp**
Start date (2/8)	**22/06/2016** [day/month/year]
End date (3/8)	**21/02/2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **30 mcg** frequency: **once per week**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: **Renal anaemia** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 21 (Concomitant Medication)

Medication (Trade name) (1/8)	**Mimpara**
Start date (2/8)	**10/05/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **30 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hyperparathyreoidism** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 22 (Concomitant Medication)

Medication (Trade name) (1/8)	**Plendil**
Start date (2/8)	**09/08/2016** [day/month/year]
End date (3/8)	**09/08/2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **5 mg** frequency: **once**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Renal Hypertension** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**

Comments (8/8)	_____ _____ _____

Instance-no: 23 (Concomitant Medication)

Medication (Trade name) (1/8)	**Bisoprolol**
Start date (2/8)	**21/02/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **2,5 mg** frequency: **4 times per week**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Renal Hypertension** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	**not on day of haemodialysis**

Instance-no: 24 (Concomitant Medication)

Medication (Trade name) (1/8)	**Citalopram**
Start date (2/8)	**21/02/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **20 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Depression** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 25 (Concomitant Medication)

Medication (Trade name) (1/8)	**Aranesp**
Start date (2/8)	**21/02/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **20 mcg** frequency: **once per week**
Route of administration (5/8)	**intranvenous**
Indication (6/8)	Medical history: **Renal anaemia** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 26 (Concomitant Medication)

Medication (Trade name) (1/8)	**Arixtra**
Start date (2/8)	**16/06/2016** [day/month/year]
End date (3/8)	**23/08/2016** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **1,5 mg** frequency: **four times per week**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: **chronic kidney disease** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**

Comments (8/8)	_____ _____ _____

Instance-no: 27 (Concomitant Medication)

Medication (Trade name) (1/8)	**Arixtra**
Start date (2/8)	**23/08/2016** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **1,5 mg** frequency: **three times per week**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: **chronic kidney disease** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 28 (Concomitant Medication)

Medication (Trade name) (1/8)	**Paspertin**
Start date (2/8)	**23/08/2016** [day/month/year]
End date (3/8)	**21/02/2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **10 mg** frequency: **three times per week**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 29 (Concomitant Medication)

Medication (Trade name) (1/8)	**Natriumthiosulfat**
Start date (2/8)	**23/06/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **25 g** frequency: **three times per week**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: _____ or Adverse event: **Relaps of calciphylaxie** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 30 (Concomitant Medication)

Medication (Trade name) (1/8)	**Mimpara**
Start date (2/8)	**31/08/2016** [day/month/year]
End date (3/8)	**19/10/2016** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **60 mg** frequency: **daily**
Route of administration (5/8)	**oral**
	Medical history: **Hyperparathyreoidism** or

Indication (6/8)	Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 31 (Concomitant Medication)

Medication (Trade name) (1/8)	**Mimpara**
Start date (2/8)	**19**/**10**/**2016** [day/month/year]
End date (3/8)	**06**/**02**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **30 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hyperparathyreoidism** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 32 (Concomitant Medication)

Medication (Trade name) (1/8)	_____
Start date (2/8)	__/__/____ [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: _____ frequency: _____
Route of administration (5/8)	_____
Indication (6/8)	Medical history: _____ or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	___
Comments (8/8)	_____ _____ _____

Adverse event [CRF-page 16/17] - Table

Instance-no: 1 (Adverse Event)

Adverse event (1/9)	**Nausea during STS-administration**
Start date (2/9)	**21**/**06**/20**16** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**related**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	[ ] None **[x] Drug treatment** [ ] Other if other - please specify: _____ _____

	_____
Outcome (8/9)	**Recovered / resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **28**/**11**/20**16** [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 2 (Adverse Event)

Adverse event (1/9)	**Emesis**
Start date (2/9)	**18**/**06**/20**16** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**probable**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	**[x] None** [ ] Drug treatment [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Recovered / resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **18**/**06**/20**16** [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 3 (Adverse Event)

Adverse event (1/9)	**cramps**
Start date (2/9)	**14**/**07**/20**16** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**not related**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	**[x] None** [ ] Drug treatment [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Recovered / resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **14**/**07**/20**16** [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 4 (Adverse Event)

Adverse event (1/9)	**Relaps of calciphylaxie**
Start date (2/9)	**23**/**06**/20**17** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**not related**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Not applicable**
Countermeasures (7/9)	[ ] None **[x] Drug treatment** [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**unknown** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: __/__/20__ [day/month/year]
Comments (9/9)	**last dose of IMP on 28.11.16**

Instance-no: 5 (Adverse Event)

Adverse event (1/9)	_____
Start date (2/9)	__/__/20__ [day/month/year]
Severity (3/9)	_____
Causal relationship to study treatment (4/9)	_____
Serious adverse event (5/9)	___ if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	_____
Countermeasures (7/9)	[ ] None [ ] Drug treatment [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	_____ if recovered/resolved or recovered/resolved with sequelae - please provide stop date: __/__/20__ [day/month/year]
Comments (9/9)	_____ _____ _____

Concomitant procedure/measure [CRF-page 17/17] - Table

Instance-no: 1 (Concomitant Procedure/Measure)

Procedure (1/5)	**Haemodialysis**
Start date (2/5)	**16**/**09**/**2014** [day/month/year]
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Indication (4/5)	Medical history/concomitant disease: **chronic kidney disease** or Adverse event: _____ or Other: _____
Comments (5/5)	_____ _____

	_____

Instance-no: 2 (Concomitant Procedure/Measure)	
Procedure (1/5)	_____
Start date (2/5)	__/__/____ [day/month/year]
End date (3/5)	__/__/____ [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: _____ or Adverse event: _____ or Other: _____
Comments (5/5)	_____ _____ _____

I confirm that I have carefully examined all entries of this patient. All information entered by myself or my colleagues is, to the best of my knowledge, correct as of the date below

Date: _____

Signature and stamp of investigator: _____

Study STS-CSM-1/13, Center: Medical University of Vienna [0103]
Patient No. 1: CRF Hardcopy, 18.09.2018 , 13:01:30

Screening/Start of run-in phase [07.04.2017]

Demographic information [CRF-page 1/17]	
Date of written informed consent (1/5)	**07**/**04**/20**17** [day/month/year]
Patient ID (2/5)	**01**-**03**-**001** (country-site-patient)
Patient year of birth (3/5)	19**61** [year] Age (at date of informed consent): **55** years
Gender (4/5)	**female**
Race of patient (5/5)	**white** if other - please specify: _____ _____ _____

Inclusion/exclusion criteria [CRF-page 2/17]	
Inclusion criteria	
Patient ⩾ 18 years (1/11)	**yes**
Male or female HD patients with a diagnosis of calciphylaxis (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching) (2/11)	**yes**
Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study (3/11)	**yes**
Exclusion criteria	
Sodium metabisulfite hypersensitivity, among others the history of bronchial asthma due to known sodium metabisulfite hypersensitivity (4/11)	**no**
Pregnant or lactating patients. As pregnancy is an extremely rare event in HD patients, a pregnancy test will only be performed in ambiguous cases. (5/11)	**no**
Females who are pregnant (positive pregnancy test at screening or during study phase) or lactating. If having reproductive potential are considered potentially ineligible with respect to use highly effective methods of birth control throughout the study. (6/11)	**no**
Patients who have participated in any other investigational studies within 30 days previous to enrollment (7/11)	**no**
History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment (8/11)	**no**
Good response to conventional treatment (9/11)	**no**
Life expectancy less than 4 months in the judgement of the investigator (10/11)	**no**
Comments (11/11)	_____ _____ _____

Clinical examination [CRF-page 3/17]	
Vital signs	
Date of assessment (1/24)	**07**/**04**/20**17** [day/month/year]
Body height (2/24)	**160** cm
Body weight (3/24)	**88** kg
Blood pressure (measured after patient has rested for 5 minutes) (4/24)	**144** mmHg / **85** mmHg [systolic/diastolic]
Heart rate (measured after patient has rested for 5 minutes) (5/24)	**97** b/min
BMI (calculated) (6/24)	**34.4** kg/m²
12-lead ECG	

ECG findings (7/24)	Date: **03**/**04**/20**17** [day/month/year] Result: **abnormal, not clinically relevant** if abnormal and clinically relevant - please specify: _____ _____ _____
Physical examination	
Were physical examinations performed (8/24)	**yes** if yes - date: **07**/**04**/20**17** [day/month/year]
Head (9/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (10/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (11/24)	**abnormal** if abnormal - please specify: **Tachycardia** if abnormal - clinically relevant: **no**
Dermatological (12/24)	**abnormal** if abnormal - please specify: **Livedo at both legs** if abnormal - clinically relevant: **yes**
Musculosceletal (13/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (14/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (15/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Neurological (16/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___

Other (17/24)	**normal** if normal or abnormal - please specify: **Vascular: pulses** if abnormal - clinically relevant: ___
Calciphylaxis diagnosis	
Calciphylaxis diagnosed according to typical signs and symptoms (18/24)	**yes** if yes - please check all that apply: **[x] Severe pain** **[x] Livedo** **[x] Violaceous plaques** [ ] Ulcerations [ ] Necroses if ulcerations and/or necroses - have other causes been excluded: ___
Tobacco use	
Tobacco use (19/24)	**Non-smoker**
Checklist	
Does the patient have any relevant medical history or concomitant diseases (20/24)	**yes**
Does the patient receive any concomitant medication (including pain medication) (21/24)	**yes**
Any concomitant procedures/measures performed (22/24)	**yes**
Has sample for biobanking been taken (23/24)	**yes** if yes - date: **07**/**04**/20**17** [day/month/year]
Comments (24/24)	**ECG was performed before Screening and inclusion to the study.**

Hematology and venous blood gas analysis [CRF-page 4/17]	
Hematology	
Date of sample (1/12)	**07**/**04**/20**17** [day/month/year]
Patient's age at sampling date (2/12)	**[x] same as at informed consent** (**55** years) or ___ years
Hemoglobin (3/12)	**9 g/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
White blood cells (4/12)	**8.74 G/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min **[x] not available**
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____.____ **mmHg** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Partial pressure of oxygen venous (8/12)	**41.7 mmHg** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Oxygen saturation (9/12)	**74.6 %** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Bicarbonate (10/12)	**22.6 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with:

	_____
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	**no arterial pO2 in venous blood gas analysis**

Clinical chemistry [CRF-page 5/17]	
Clinical Chemistry	
Date of sample (1/25)	**07**/**04**/20**17** [day/month/year]
Patient's age at sampling date (2/25)	**[x] same as at informed consent** (**55** years) or ___ years
IPTH (3/25)	**398.7 pg/ml** if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
Calcium (4/25)	**2.23 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Phosphate (5/25)	**1.38 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Alk. phosphatase (6/25)	**112 U/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
pH serum (7/25)	**7.37 1/1** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	**8.5 mg/dl** if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **other**
Creatinine (9/25)	**3.52 mg/dl** if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
Albumin (10/25)	**26.9 g/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Sodium (11/25)	**136 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Potassium (12/25)	**3.6 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Chloride (13/25)	**95 mmol/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Magnesium (14/25)	**0.72 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GOT (AST) (15/25)	**19 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
	14 U/l

GPT (ALT) (16/25)	if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Gamma-GT (17/25)	**86 U/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Amylase (18/25)	**39 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Lipase (19/25)	**47 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Urea (20/25)	**9.6 mg/dl** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Uric acid (21/25)	**0.9 mg/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	**17 pg/ml** if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
25-Hydroxy-Vitamin D (23/25)	**17.8 nmol/l** if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
If "other" was chosen above for at least one time - please specify (24/25)	**Infection of unknown origin**
Comments (25/25)	_____ _____ _____

Wound, pain and other assessments [CRF-page 6/17]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/4)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/4)	**yes** if yes - degree of pain: **40** mm
Pregnancy test	
Pregnancy test (3/4)	**not applicable (e.g. menopause, hysterectomy)** Date:__/__/20__ [day/month/year]
Comments (4/4)	_____ _____ _____

End of run-in phase

Inclusion/exclusion criteria [CRF-page 7/17]	
Inclusion criteria	
Patient $\geqslant$ 18 years (1/11)	**yes**
Male or female HD patients with a diagnosis of calciphylaxis. (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching). (2/11)	**yes**
Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study (3/11)	**yes**

Exclusion criteria	
Sodium metabisulfite hypersensitivity, among others the history of bronchial asthma due to known sodium metabisulfite hypersensitivity (4/11)	**no**
Pregnant or lactating patients. As pregnancy is an extremely rare event in HD patients, a pregnancy test will only be performed in ambiguous cases. (5/11)	**no**
Females who are pregnant (positive pregnancy test at screening or during study phase) or lactating. If having reproductive potential are considered potentially ineligible with respect to use highly effective methods of birth control throughout the study. (6/11)	**no**
Patients who have participated in any other investigational studies within 30 days previous to enrollment (7/11)	**no**
History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment (8/11)	**no**
Good response to conventional treatment (9/11)	**no**
Life expectancy less than 4 months in the judgement of the investigator (10/11)	**no**
Comments (11/11)	_____ _____ _____

Completion of run-in-phase [CRF-page 8/17]	
Biopsy report of consisting wound available (1/7)	**yes** if yes: please check all that apply: [ ] none **[x] diagnosis of calciphylaxis confirmed** [ ] other causes for necroses and ulcerations excluded
Has a skin biopsy been taken (2/7)	**yes** if yes, date:**05**/**04**/20**17** [day/month/year] if yes - calciphylaxis diagnosis confirmed by analysis: **yes**
Has the patient agreed to participate in the clinical trial and to undergo STS treatment (3/7)	**yes**
Disease status under BSC (4/7)	**rapidly progressive disease**
Have all screening/baseline assessments been performed and is patient considered eligible for treatment start (5/7)	**yes** if no - please check all that apply: [ ] patient did not meet all in-/exclusion criteria [ ] withdrawal of informed consent by the patient [ ] discretion of the investigator [ ] calciphylaxis diagnosis not confirmed [ ] other reason if other reason - please specify: _____ _____ _____
Comments (6/7)	**Biopsy was performed before inclusion to the study (routine procedure, independent of the study).**

Visits

Visits [CRF-page 9/17] - Table	
Instance-no: 1 (Visits)	
Visit 0 Start of visit [Instance-no: 1, page 1/5]	
Actual date of visit (1/6)	**10**/**04**/20**17** [day/month/year] [ ] not done
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (2/6)	**yes**
Any new concomitant procedures/measures or changes in	**no**

concomitant procedures/measures (3/6)	
Any new adverse events or changes in adverse events (4/6)	**yes**
Soft tissue radiographs	
Have soft tissue radiographs been taken (optional) (5/6)	**no** if yes, date: __/__/20__ [day/month/year]
Comments (6/6)	_____ _____ _____
Clinical examination [Instance-no: 1, page 2/5]	
Vital signs	
Date of assessment (1/17)	**10**/**04**/20**17** [day/month/year]
Body weight (2/17)	**85** kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	**155** mmHg / **80** mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	**102** b/min [ ] not done
BMI (calculated) (5/17)	**33.2** kg/m²
Physical examination	
Were physical examinations performed (6/17)	**yes** if yes - date: **10**/**04**/20**17** [day/month/year]
Head (7/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (8/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (9/17)	**abnormal** if abnormal - please specify: **Tachycardia** if abnormal - clinically relevant: **no**
Dermatological (10/17)	**abnormal** if abnormal - please specify: **Skin Lesions and livedo at both legs** if abnormal - clinically relevant: **yes**
Musculosceletal (11/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (12/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
	normal if abnormal - please specify:

Gastrointestinal (13/17)	_____ _____ _____ if abnormal - clinically relevant: ___
Neurological (14/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Other (15/17)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Biobanking	
Has sample for biobanking been taken (16/17)	**no** if yes - date: __/__/20__ [day/month/year]
Comments (17/17)	**Due to the short interval of 3 days between VR and VO, it was discussed and decided, that no new blood samples are necessary at this visit.**
Hematology and venous blood gas analysis [Instance-no: 1, page 3/5]	
Hematology	
Date of sample (1/12)	**10**/**04**/20**17** [day/month/year]
Patient's age at sampling date (2/12)	**[x] same as at informed consent** (**55** years) or ___ years
Hemoglobin (3/12)	**8.7 g/dl** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **medical history**
White blood cells (4/12)	**11.56 G/l** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **medical history**
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min **[x] not available**
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	_____.____ **mmHg [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Bicarbonate (8/12)	_____.____ **mmol/l [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (9/12)	_____ _____ _____
Comments (10/12)	**not done after agreement with the sponsor**
Clinical chemistry [Instance-no: 1, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	**10**/**04**/20**17** [day/month/year]
Patient's age at sampling date (2/25)	**[x] same as at informed consent** (**55** years) or ___ years
	_____.____ **pg/ml [x] not available**

IPTH (3/25)	if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Calcium (4/25)	**2.17 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Phosphate (5/25)	**1.56 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
Alk. phosphatase (6/25)	_____._____ **U/l [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
pH serum (7/25)	_____._____ **1/1 [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	**6.77 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **medical history**
Creatinine (9/25)	**6.21 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
Albumin (10/25)	**22.7 g/l** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
Sodium (11/25)	**137 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Potassium (12/25)	**3.65 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Chloride (13/25)	**96 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Magnesium (14/25)	**0.76 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GOT (AST) (15/25)	_____._____ **U/l [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GPT (ALT) (16/25)	_____._____ **U/l [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Gamma-GT (17/25)	_____._____ **U/l [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Amylase (18/25)	_____._____ **U/l [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Lipase (19/25)	_____._____ **U/l [x] not available** if outside normal limits - clinically relevant ? ___

	if clinically relevant - causal relationship with: _____
Urea (20/25)	**21.9 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Uric acid (21/25)	_____.____ **mg/dl [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	_____.____ **pg/ml [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
25-Hydroxy-Vitamin D (23/25)	_____.____ **nmol/l [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	**not done completely after agreement with the sponsor**
Wound, pain and other assessments [Instance-no: 1, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	**yes** if yes - degree of pain: **7** mm
Pregnancy test	
Pregnancy test (3/6)	**not done** Date:__/__/20__ [day/month/year]
Bone Mineral Density	
Has bone mineral density been assessed (4/6)	**no** if yes: method:_____ t-score:__.__ z-score:__.__
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (5/6)	**yes** if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: **moderately ill**
Comments (6/6)	_____ _____ _____

Instance-no: 2 (Visits)

Visit 1 Start of visit [Instance-no: 2, page 1/3]	
Planned date of visit (1/7)	08/05/2017 [day/month/year]
Actual date of visit (2/7)	**12**/**05**/20**17** [day/month/year] [ ] not done if deviation from planned date - please provide reason: **ongoing week 4 after inclusion**
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	**yes**
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	**yes**
Any new adverse events or changes in adverse events (5/7)	**yes**

Any new lesions under STS treatment (6/7)	**no**
Comments (7/7)	_____ _____ _____
Clinical examination [Instance-no: 2, page 2/3]	
Vital signs	
Date of assessment (1/16)	**12**/**05**/20**17** [day/month/year]
Body weight (2/16)	**83.8** kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/16)	**132** mmHg / **90** mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/16)	**80** b/min [ ] not done
BMI (calculated) (5/16)	**32.7** kg/m²
Physical examination	
Were physical examinations performed (6/16)	**yes** if yes - date: **12**/**05**/20**17** [day/month/year]
Head (7/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (8/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (9/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Dermatological (10/16)	**abnormal** if abnormal - please specify: **Calciphylaxia related necrosis on both lower limbs.** if abnormal - clinically relevant: **yes**
Musculosceletal (11/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (12/16)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (13/16)	**normal** if abnormal - please specify: _____ _____

	_____ if abnormal - clinically relevant: ___
Neurological (14/16)	**not done** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Other (15/16)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Comments (16/16)	_____ _____ _____
Wound, pain and other assessments [Instance-no: 2, page 3/3]	
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (1/5)	**yes** if yes - degree of pain: **70** mm
Pregnancy test	
Pregnancy test (2/5)	**not applicable (e.g. menopause, hysterectomy)** Date:__/__/20__ [day/month/year]
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (3/5)	**yes** if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: **markedly ill**
Was the clinical global impression improvement assessed using the CGI-I-score (4/5)	**yes** if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: **much worse**
Comments (5/5)	**Due to necrosis of the wounds and necessary necrosectmia, the patient's clinical impession is worse**

Instance-no: 3 (Visits)

Visit 2 Start of visit [Instance-no: 3, page 1/5]	
Planned date of visit (1/7)	05/06/2017 [day/month/year]
Actual date of visit (2/7)	**09**/**06**/20**17** [day/month/year] [ ] not done if deviation from planned date - please provide reason: **Week 8**
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	**yes**
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	**yes**
Any new adverse events or changes in adverse events (5/7)	**yes**
Any new lesions under STS treatment (6/7)	**no**
Comments (7/7)	_____ _____ _____
Clinical examination [Instance-no: 3, page 2/5]	
Vital signs	

Date of assessment (1/17)	**09**/**06**/20**17** [day/month/year]
Body weight (2/17)	___._ kg **[x] not done**
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	**110** mmHg / **60** mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	**80** b/min [ ] not done
BMI (calculated) (5/17)	___._ kg/m²
Physical examination	
Were physical examinations performed (6/17)	**yes** if yes - date: **09**/**06**/20**17** [day/month/year]
Head (7/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (8/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (9/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Dermatological (10/17)	**abnormal** if abnormal - please specify: **big wounds after debridement, plastic surgical split skin graft** if abnormal - clinically relevant: **yes**
Musculosceletal (11/17)	**abnormal** if abnormal - please specify: **muscular weekness** if abnormal - clinically relevant: **no**
Respiratory (12/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (13/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Neurological (14/17)	**not done** if abnormal - please specify: _____ _____ _____

	if abnormal - clinically relevant: ___
Other (15/17)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Biobanking	
Has sample for biobanking been taken (16/17)	**yes** if yes - date: **09**/**06**/20**17** [day/month/year]
Comments (17/17)	_____ _____ _____
Hematology and venous blood gas analysis [Instance-no: 3, page 3/5]	
Hematology	
Date of sample (1/12)	**09**/**06**/20**17** [day/month/year]
Patient's age at sampling date (2/12)	**[x] same as at informed consent** (**55** years) or ___ years
Hemoglobin (3/12)	**8.7 g/dl** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **medical history**
White blood cells (4/12)	**10.75 G/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min **[x] not available**
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	**44.7 mmHg** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Bicarbonate (8/12)	**17.3 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
If "other" was chosen above for at least one time - please specify (9/12)	_____ _____ _____
Comments (10/12)	_____ _____ _____
Clinical chemistry [Instance-no: 3, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	**09**/**06**/20**17** [day/month/year]
Patient's age at sampling date (2/25)	**[x] same as at informed consent** (**55** years) or ___ years
IPTH (3/25)	_____.____ **pg/ml [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Calcium (4/25)	**2.27 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Phosphate (5/25)	**1.81 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with:

	underlying disease
Alk. phosphatase (6/25)	**1033 U/l** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **other**
pH serum (7/25)	**7.3 1/1** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
C-reactive protein (CRP) (8/25)	**10.66 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **other**
Creatinine (9/25)	**6.65 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
Albumin (10/25)	**17.7 g/l** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
Sodium (11/25)	**142 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Potassium (12/25)	**5.24 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
Chloride (13/25)	**92 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Magnesium (14/25)	**0.98 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GOT (AST) (15/25)	**91 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
GPT (ALT) (16/25)	**35 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Gamma-GT (17/25)	**2075 U/l** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **other**
Amylase (18/25)	**4 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Lipase (19/25)	**13 U/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Urea (20/25)	**17.6 mg/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Uric acid (21/25)	**7.5 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____

1,25-Dihydroxy-Vitamine D (22/25)	_____._____ **pg/ml [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
25-Hydroxy-Vitamin D (23/25)	_____._____ **nmol/l [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (24/25)	**CRP is elevated after surgery AP and yGT is elevated in cholestasis (adverse event)**
Comments (25/25)	_____ _____ _____
Wound, pain and other assessments [Instance-no: 3, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/6)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/6)	**yes** if yes - degree of pain: **48** mm
Pregnancy test	
Pregnancy test (3/6)	**not applicable (e.g. menopause, hysterectomy)** Date:__/__/20__ [day/month/year]
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (4/6)	**yes** if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time: **markedly ill**
Was the clinical global impression improvement assessed using the CGI-I-score (5/6)	**yes** if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: **minimally worse**
Comments (6/6)	_____ _____ _____

Instance-no: 4 (Visits)

Visit 3 Start of visit [Instance-no: 4, page 1/1]	
Planned date of visit (1/7)	31/07/2017 [day/month/year]
Actual date of visit (2/7)	__/__/20__ [day/month/year] **[x] not done** if deviation from planned date - please provide reason: _____ _____ _____
Comments (3/7)	**Data from V3 moved to end-of-study visit V6**

Instance-no: 5 (Visits)

Visit 4 Start of visit [Instance-no: 5, page 1/1]	
Planned date of visit (1/7)	25/09/2017 [day/month/year]
Actual date of visit (2/7)	__/__/20__ [day/month/year] **[x] not done** if deviation from planned date - please provide reason: _____ _____ _____
Comments (3/7)	_____ _____ _____

Instance-no: 6 (Visits)

Visit 5 Start of visit [Instance-no: 6, page 1/1]	
Planned date of visit (1/7)	18/12/2017 [day/month/year]

Actual date of visit (2/7)	__/__/20__ [day/month/year] **[x] not done** if deviation from planned date - please provide reason: _____ _____ _____
Comments (3/7)	_____ _____ _____

Instance-no: 7 (Visits)

Visit 6 Start of visit [Instance-no: 7, page 1/5]	
Planned date of visit (1/7)	12/03/2018 [day/month/year]
Actual date of visit (2/7)	**31**/**07**/20**17** [day/month/year] [ ] not done if deviation from planned date - please provide reason: **End of study because of drop out**
Checklist	
Any new concomitant medications or changes in concomitant medications (including pain medication) (3/7)	**yes**
Any new concomitant procedures/measures or changes in concomitant procedures/measures (4/7)	**no**
Any new adverse events or changes in adverse events (5/7)	**yes**
Any new lesions under STS treatment (6/7)	**no**
Comments (7/7)	**End of study**
Clinical examination [Instance-no: 7, page 2/5]	
Vital signs	
Date of assessment (1/17)	**31**/**07**/20**17** [day/month/year]
Body weight (2/17)	**74** kg [ ] not done
Blood pressure (measured after patient has rested for 5 minutes) (3/17)	**130** mmHg / **80** mmHg [systolic/diastolic] [ ] not done
Heart rate (measured after patient has rested for 5 minutes) (4/17)	**90** b/min [ ] not done
BMI (calculated) (5/17)	**28.9** kg/m²
Physical examination	
Were physical examinations performed (6/17)	**yes** if yes - date: **31**/**07**/20**17** [day/month/year]
Head (7/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (8/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (9/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
	abnormal

Dermatological (10/17)	if abnormal - please specify: **lesions on both lower limbs with split skin grafts** if abnormal - clinically relevant: **yes**
Musculosceletal (11/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (12/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (13/17)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Neurological (14/17)	**not done** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Other (15/17)	**not done** if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Biobanking	
Has sample for biobanking been taken (16/17)	**yes** if yes - date: **31**/**07**/20**17** [day/month/year]
Comments (17/17)	_____ _____ _____
Hematology and venous blood gas analysis [Instance-no: 7, page 3/5]	
Hematology	
Date of sample (1/12)	**31**/**07**/20**17** [day/month/year]
Patient's age at sampling date (2/12)	**[x] same as at informed consent** (**55** years) or ___ years
Hemoglobin (3/12)	**10.1 g/dl** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
White blood cells (4/12)	**6.33 G/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____

T50 Test (6/12)	___ min **[x] not available**
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	**35.3 mmHg** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Bicarbonate (8/12)	**23.5 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (9/12)	_____ _____ _____
Comments (10/12)	_____ _____ _____
Clinical chemistry [Instance-no: 7, page 4/5]	
Clinical Chemistry	
Date of sample (1/25)	**31**/**07**/20**17** [day/month/year]
Patient's age at sampling date (2/25)	**[x] same as at informed consent** (**55** years) or ___ years
IPTH (3/25)	**61.8 pg/ml** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Calcium (4/25)	**2.4 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Phosphate (5/25)	**1.11 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Alk. phosphatase (6/25)	**711 U/l** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **medical history**
pH serum (7/25)	**7.37 1/1** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	**5.94 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **other**
Creatinine (9/25)	**4.36 mg/dl** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
Albumin (10/25)	**20.3 g/l** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
Sodium (11/25)	**126 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Potassium (12/25)	**3.45 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Chloride (13/25)	**91 mmol/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____

Magnesium (14/25)	**0.71 mmol/l** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GOT (AST) (15/25)	**149 U/l** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **other**
GPT (ALT) (16/25)	**52 U/l** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **other**
Gamma-GT (17/25)	**1329 U/l** [ ] not available if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **other**
Amylase (18/25)	**4 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Lipase (19/25)	**8 U/l** [ ] not available if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Urea (20/25)	**9.2 mg/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Uric acid (21/25)	**5.6 mg/dl** [ ] not available if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	_____.____ **pg/ml [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
25-Hydroxy-Vitamin D (23/25)	_____.____ **nmol/l [x] not available** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (24/25)	**adverse event #10 and #13**
Comments (25/25)	**End of study because of drop out. Because of icteric and lipemic blood sample, Vit. D is not available**
Wound, pain and other assessments [Instance-no: 7, page 5/5]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/7)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/7)	**yes** if yes - degree of pain: **20** mm
Pregnancy test	
Pregnancy test (3/7)	**not applicable (e.g. menopause, hysterectomy)** Date:__/__/20__ [day/month/year]
Bone Mineral Density	
Has bone mineral density been assessed (4/7)	**no** if yes: method:_____ t-score:__.__ z-score:__.__
Clinical Global Impression	
Was the clinical global impression severity assessed using the CGI-S-scale (5/7)	**yes** if yes: Considering your total clinical experience with this particular population, how ill is the patient at this time:

	markedly ill
Was the clinical global impression improvement assessed using the CGI-I-score (6/7)	**yes** if yes: Compared to the patient's condition at the baseline visit (V0), this patient's condition is: **minimally improved**
Comments (7/7)	_____ _____ _____

Study medication

Study medication [CRF-page 10/17] - Table	
Instance-no: 1 (Study Medication)	
Dosage (1/5)	**25** g **3** times a week
Dosage start date (2/5)	**10**/**04**/20**17** [day/month/year]
Dosage stop date (3/5)	**19**/**06**/20**17** [day/month/year] or [ ] currently ongoing
Number of administrations with this dosage (4/5)	**30**
Comments (5/5)	_____ _____ _____
Instance-no: 2 (Study Medication)	
Dosage (1/6)	**12.5** g **3** times a week
Dosage start date (2/6)	**19**/**06**/20**17** [day/month/year]
Dosage stop date (3/6)	**26**/**06**/20**17** [day/month/year] or [ ] currently ongoing
Number of administrations with this dosage (4/6)	**4**
Reason for dosage change (5/6)	**Nausea, Cholestasis**
Comments (6/6)	_____ _____ _____
Instance-no: 3 (Study Medication)	
Dosage (1/6)	**12.5** g **3** times a week
Dosage start date (2/6)	**11**/**07**/20**17** [day/month/year]
Dosage stop date (3/6)	**12**/**07**/20**17** [day/month/year] or [ ] currently ongoing
Number of administrations with this dosage (4/6)	**1**
Reason for dosage change (5/6)	**Vomiting**
Comments (6/6)	_____ _____ _____
Instance-no: 4 (Study Medication)	
Dosage (1/6)	___**.**__ g _ times a week
Dosage start date (2/6)	__/__/20__ [day/month/year]
Dosage stop date (3/6)	__/__/20__ [day/month/year] or [ ] currently ongoing
Number of administrations with this dosage (4/6)	___
Reason for dosage change (5/6)	_____ _____ _____
Comments (6/6)	_____ _____ _____

Lesions

Lesions [CRF-page 11/17] - Table	
Instance-no: 1 (Lesions)	
Lesion (1/25)	Lesion number: **1** Lesion location: **left limb, tibial**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	__/__/20__ [day/month/year] or **[x] still present**
revised PWAT	

Photodocumentation VR (Run-in-phase) (4/25)	Date: **07**/**04**/20**17** [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **13.2** cm^2 or [ ] Wound area not assessed Size: **3** Depth: **1** Necrotic tissue type: **1** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **3** Total score: **22**
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **8.9** cm^2 or [ ] Wound area not assessed Size: **2** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **0** Total score: **2**
Photodocumentation V0 (7/25)	Date: **10**/**04**/20**17** [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **27.1** cm^2 or [ ] Wound area not assessed Size: **4** Depth: **1** Necrotic tissue type: **2** Total amount of necrotic tissue: **3** Granulation tissue type: **3** Total amount of granulation tissue: **4** Edges: **1** Periulcer skin viability: **3** Total score: **21**
	Initials Dermatologist: **J** / **K** [first/last name]

Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **1** Total score: **1**
Photodocumentation V2 (10/25)	Date: **09**/**06**/20**17** [day/month/year] or _____
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **1.9** cm^2 or [ ] Wound area not assessed Size: **1** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **3** Periulcer skin viability: **2** Total score: **24**
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **4** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **0** Total score: **4**
Photodocumentation V3 (13/25)	Date: **31**/**07**/20**17** [day/month/year] or _____
	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **89** cm^2 or [ ] Wound area not assessed

Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Size: **4** Depth: **1** Necrotic tissue type: **3** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **3** Periulcer skin viability: **3** Total score: **26**
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **0** cm^2 or [ ] Wound area not assessed Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **2** Periulcer skin viability: **0** Total score: **2**
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth:

Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	_ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _

Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	_____ _____ _____

Instance-no: 2 (Lesions)

Lesion (1/25)	Lesion number: **2** Lesion location: **left limb, calf**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	__/__/20__ [day/month/year] or **[x] still present**
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **07**/**04**/20**17** [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **9.1** cm^2 or [ ] Wound area not assessed Size: **3** Depth: **1** Necrotic tissue type: **3** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **3** Total score: **24**
	Initials Dermatologist: **J** / **K** [first/last name]

Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **1** Total score: **1**
Photodocumentation V0 (7/25)	Date: **10**/**04**/20**17** [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **1.9** cm^2 or [ ] Wound area not assessed Size: **1** Depth: **1** Necrotic tissue type: **1** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **3** Total score: **20**
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **8.81** cm^2 or [ ] Wound area not assessed Size: **2** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **0** Total score: **2**
Photodocumentation V2 (10/25)	Date: **09**/**06**/20**17** [day/month/year] or _____
	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **8.1** cm^2 or [ ] Wound area not assessed

Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Size: **2** Depth: **1** Necrotic tissue type: **1** Total amount of necrotic tissue: **4** Granulation tissue type: **2** Total amount of granulation tissue: **4** Edges: **3** Periulcer skin viability: **2** Total score: **19**
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **4** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **2** Periulcer skin viability: **0** Total score: **6**
Photodocumentation V3 (13/25)	Date: **31**/**07**/20**17** [day/month/year] or _____
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **5.8** cm^2 or [ ] Wound area not assessed Size: **2**

Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Depth: **1** Necrotic tissue type: **1** Total amount of necrotic tissue: **1** Granulation tissue type: **1** Total amount of granulation tissue: **1** Edges: **2** Periulcer skin viability: **1** Total score: **10**
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type:

Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	_ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type:

	_ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	**Wound assessment and revPWAT V3 not done by Dermatologist M. L.**

Instance-no: 3 (Lesions)

Lesion (1/25)	Lesion number: **3** Lesion location: **right limb, tibial**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	__/__/20__ [day/month/year] or **[x] still present**
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **07**/**04**/20**17** [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **6** cm^2 or [ ] Wound area not assessed Size: **2** Depth: **1** Necrotic tissue type: **1** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **1** Periulcer skin viability: **3** Total score: **20**
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **1** Total score: **1**
Photodocumentation V0 (7/25)	Date: **10**/**04**/20**17** [day/month/year] or _____
	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **7.5** cm^2 or [ ] Wound area not assessed Size:

Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	**2** Depth: **1** Necrotic tissue type: **3** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **1** Periulcer skin viability: **3** Total score: **22**
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **1** Total score: **1**
Photodocumentation V2 (10/25)	Date: **09**/**06**/20**17** [day/month/year] or _____
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **0.75** cm^2 or [ ] Wound area not assessed Size: **1** Depth: **1** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **1** Total amount of granulation tissue: **1** Edges: **3** Periulcer skin viability: **1** Total score: **8**
	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **0** Depth: **0**

Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **0** Total score: **0**
Photodocumentation V3 (13/25)	Date: **31**/**07**/20**17** [day/month/year] or _____
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **1.2** cm^2 or [ ] Wound area not assessed Size: **1** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **3** Periulcer skin viability: **1** Total score: **23**
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **0** Total score: **0**
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _

Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _

	Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	_____ _____ _____

Instance-no: 4 (Lesions)

Lesion (1/25)	Lesion number: **4** Lesion location: **right limb, calf**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	__/__/20__ [day/month/year] or **[x] still present**
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **07**/**04**/20**17** [day/month/year] or _____
	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **2.4** cm^2 or [ ] Wound area not assessed Size:

Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	**2** Depth: **1** Necrotic tissue type: **1** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **3** Total score: **21**
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **0** Depth: **0** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **1** Total score: **1**
Photodocumentation V0 (7/25)	Date: **10**/**04**/20**17** [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **4.8** cm^2 or [ ] Wound area not assessed Size: **2** Depth: **1** Necrotic tissue type: **1** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **3** Periulcer skin viability: **3** Total score: **22**
	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **4.8** cm^2 or [ ] Wound area not assessed Size: **2** Depth: **0**

Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **0** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **1** Total score: **3**
Photodocumentation V2 (10/25)	Date: **09**/**06**/20**17** [day/month/year] or _____
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **60** cm^2 or [ ] Wound area not assessed Size: **4** Depth: **1** Necrotic tissue type: **1** Total amount of necrotic tissue: **1** Granulation tissue type: **1** Total amount of granulation tissue: **1** Edges: **3** Periulcer skin viability: **2** Total score: **14**
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **4** Depth: **3** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **1** Total amount of granulation tissue: **1** Edges: **1** Periulcer skin viability: **0** Total score: **10**
Photodocumentation V3 (13/25)	Date: **31**/**07**/20**17** [day/month/year] or _____
	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **63** cm^2 or [ ] Wound area not assessed Size: **4** Depth: **3** Necrotic tissue type:

Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	_ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: **3** Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **4** cm^2 or [ ] Wound area not assessed Size: **2** Depth: **1** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **3** Total amount of granulation tissue: **1** Edges: **1** Periulcer skin viability: **0** Total score: **8**
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type:

	_ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _

	Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	**Assessment not completely filled in for Wound assessment and revPWAT V3 by M. L.**

Instance-no: 5 (Lesions)

Lesion (1/25)	Lesion number: __ Lesion location: _____
Date of occurrence (2/25)	__/__/20__ [day/month/year] or [ ] before study start
Date of healing (3/25)	__/__/20__ [day/month/year] or [ ] still present
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _

Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V0 (7/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V2 (10/25)	Date: __/__/20__ [day/month/year] or _____
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue:

Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	_ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _

	Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue:

	_ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _

	Periulcer skin viability: _ Total score: __
Comments (25/25)	_____ _____ _____

Follow-up telephone interviews

Follow-up telephone interviews [CRF-page 12/17] - Table	
Instance-no: 1 (Follow-up telephone interviews)	
Follow-up telephone interview 1 Patient status [Instance-no: 1, page 1/1]	
Date of telephone call (1/7)	__/__/20__ [day/month/year]
Survival status	
Patient alive (2/7)	___
Disease status	
Is the disease still present (3/7)	___
Continuation STS-treatment	
Has the patient received further STS-treatment since last visit (4/7)	___
Further treatment	
Any further or additional treatment (5/7)	___
New calciphylaxis medication	
Any new medication for treatment of calciphylaxis (6/7)	___
Comments (7/7)	_____ _____ _____

End of study [31.07.2017]

End of study [CRF-page 13/17]	
Date of study end (1/6)	**31**/**07**/20**17** [day/month/year]
Has the patient been listed on a transplant waiting list (2/6)	**no** if yes, date: __/__/20__ [day/month/year]
Date of last contact when patient was alive (3/6)	**31**/**07**/20**17** [day/month/year]
Reason of study end (4/6)	**early discontinuation** if early discontinuation, lost to follow-up or other - please specify: **Side effects: Nausea, Emesis Severe illness: drug induced liver injury, not necessary medication was stopped.** if patient died - date of death: __/__/20__ [day/month/year] [ ] not available reason of death: _____ if other reason - please specify: _____ _____ _____
Has all patient data been entered as far as possible and checked, all data can be set read-only (5/6)	**yes**
Comments (6/6)	_____ _____ _____

Medical history, concomitant medication and procedures, adverse events

Medical history [CRF-page 14/17] - Table	
Instance-no: 1 (Medical History)	
Condition (1/5)	**Hypertension**
Start date (2/5)	__/__/**1989** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**

Treated with medications at study start (4/5)	**yes**
Comments (5/5)	**Exact start date is unknown**

Instance-no: 2 (Medical History)

Condition (1/5)	**Diabetes mellitus**
Start date (2/5)	__/__/**2001** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	**exact start date is unknown**

Instance-no: 3 (Medical History)

Condition (1/5)	**immune complex glomerulonephritis**
Start date (2/5)	**19/01/2017** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____

Instance-no: 4 (Medical History)

Condition (1/5)	**kidney transplantation**
Start date (2/5)	**18/09/2001** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 5 (Medical History)

Condition (1/5)	**Infection of unknown origin**
Start date (2/5)	**03/04/2017** [day/month/year] or [ ] unknown
End date (3/5)	**18/04/2017** [day/month/year] or _____
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 6 (Medical History)

Condition (1/5)	**C. difficile–associated diarrhea**
Start date (2/5)	**06/04/2017** [day/month/year] or [ ] unknown
End date (3/5)	**17/04/2017** [day/month/year] or _____
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 7 (Medical History)

Condition (1/5)	**Depressive episodes**
Start date (2/5)	__/__/**2010** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	**exact start date is unknown**

Instance-no: 8 (Medical History)

Condition (1/5)	**Hyperlipidemia**
Start date (2/5)	__/__/**2001** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	**exact start date is unknown**

Instance-no: 9 (Medical History)

Condition (1/5)	**Calciphylaxis**
Start date (2/5)	**03/04/2017** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____

Instance-no: 10 (Medical History)

Condition (1/5)	**Renal transplant failure**
Start date (2/5)	**03/04/2017** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	**Dialysis**

Instance-no: 11 (Medical History)

Condition (1/5)	_____
Start date (2/5)	__/__/____ [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or _____
Treated with medications at study start (4/5)	___
Comments (5/5)	_____ _____ _____

Concomitant medication [CRF-page 15/17] - Table

Instance-no: 1 (Concomitant Medication)

Medication (Trade name) (1/8)	**Dilatrend**
Start date (2/8)	__/**11/2016** [day/month/year]
End date (3/8)	**28/06/2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **50 mg** frequency: **2**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hypertension** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	**exact start date unknown.**

Instance-no: 2 (Concomitant Medication)

Medication (Trade name) (1/8)	**Syscor**
Start date (2/8)	**28/08/1998** [day/month/year]
End date (3/8)	**21/04/2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **5 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hypertension** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 3 (Concomitant Medication)

Medication (Trade name) (1/8)	**Renitec**
Start date (2/8)	**21/09/2001** [day/month/year]

End date (3/8)	**07**/**04**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **20 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hypertension** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 4 (Concomitant Medication)

Medication (Trade name) (1/8)	**Sortis**
Start date (2/8)	**12**/**12**/**2001** [day/month/year]
End date (3/8)	**07**/**04**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **40 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hyperlipidemia** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 5 (Concomitant Medication)

Medication (Trade name) (1/8)	**Diamicron**
Start date (2/8)	__/__/**2010** [day/month/year]
End date (3/8)	**07**/**04**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **90 mg** frequency: **2-0-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Diabetes mellitus** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	**start date is unknown**

Instance-no: 6 (Concomitant Medication)

Medication (Trade name) (1/8)	**Xanor**
Start date (2/8)	__/__/**2010** [day/month/year]
End date (3/8)	**14**/**07**/**2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **0,5 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Depressive episodes** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	**exact start date is unknown**

Instance-no: 7 (Concomitant Medication)

Medication (Trade name) (1/8)	**Toujeo (Insulin glargin)**
Start date (2/8)	**15**/**12**/**2016** [day/month/year]
	06/**06**/**2017** [day/month/year] or

End date (3/8)	_____
Dose and frequency (4/8)	total daily dose and unit: **42 IE** frequency: **daily**
Route of administration (5/8)	**s.c.**
Indication (6/8)	Medical history: **Diabetes mellitus** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 8 (Concomitant Medication)

Medication (Trade name) (1/8)	**Insulin Humalog**
Start date (2/8)	**06/12/2016** [day/month/year]
End date (3/8)	**06/06/2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **48 IE** frequency: **1-1-1**
Route of administration (5/8)	**s.c.**
Indication (6/8)	Medical history: **Diabetes mellitus** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 9 (Concomitant Medication)

Medication (Trade name) (1/8)	**Lasix**
Start date (2/8)	**07/03/2017** [day/month/year]
End date (3/8)	**27/04/2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **250 mg** frequency: **1/4-1/4-0**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **immune complex glomerulonephritis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 10 (Concomitant Medication)

Medication (Trade name) (1/8)	**Ixel**
Start date (2/8)	**07/03/2017** [day/month/year]
End date (3/8)	**26/04/2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **25 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Depressive episodes** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 11 (Concomitant Medication)

Medication (Trade name) (1/8)	**Aranesp**
Start date (2/8)	**07**/**03**/**2017** [day/month/year]
End date (3/8)	**11**/**04**/**2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **25 mcg** frequency: **once a week**
Route of administration (5/8)	**s.c.**
Indication (6/8)	Medical history: **immune complex glomerulonephritis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 12 (Concomitant Medication)

Medication (Trade name) (1/8)	**Metronidazol**
Start date (2/8)	**07**/**04**/**2017** [day/month/year]
End date (3/8)	**17**/**04**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **1000 mg** frequency: **1-0-1**
Route of administration (5/8)	**i.v.**
Indication (6/8)	Medical history: **C. difficile–associated diarrhea** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 13 (Concomitant Medication)

Medication (Trade name) (1/8)	**Unasyn (Ampicillin/Sulbactam)**
Start date (2/8)	**04**/**04**/**2017** [day/month/year]
End date (3/8)	**18**/**04**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **6g** frequency: **post HD**
Route of administration (5/8)	**i.v.**
Indication (6/8)	Medical history: **Infection of unknown origin** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 14 (Concomitant Medication)

Medication (Trade name) (1/8)	**Sandimmun**
Start date (2/8)	**18**/**09**/**2001** [day/month/year]
End date (3/8)	**05**/**04**/**2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **150 mg** frequency: **1-0-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **kidney transplantation** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____

	_____

Instance-no: 15 (Concomitant Medication)

Medication (Trade name) (1/8)	**CellCept**
Start date (2/8)	**18**/**09**/**2001** [day/month/year]
End date (3/8)	**06**/**04**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **2000 mg** frequency: **1-0-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **kidney transplantation** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 16 (Concomitant Medication)

Medication (Trade name) (1/8)	**Aprednislon**
Start date (2/8)	**02**/**09**/**2002** [day/month/year]
End date (3/8)	**07**/**04**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **5 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **kidney transplantation** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 17 (Concomitant Medication)

Medication (Trade name) (1/8)	**Renvela**
Start date (2/8)	**06**/**04**/**2017** [day/month/year]
End date (3/8)	**17**/**04**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **2400 mg** frequency: **1-1-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **immune complex glomerulonephritis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 18 (Concomitant Medication)

Medication (Trade name) (1/8)	**Hydal**
Start date (2/8)	**08**/**04**/**2017** [day/month/year]
End date (3/8)	**27**/**05**/**2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **4 mg** frequency: **1-0-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____

Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	**Calciphylaxie**

Instance-no: 19 (Concomitant Medication)

Medication (Trade name) (1/8)	**Zofran (Ondansetron)**
Start date (2/8)	**10**/**04**/**2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **8 mg** frequency: **When required**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **Nausea** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 20 (Concomitant Medication)

Medication (Trade name) (1/8)	**Sedacoron**
Start date (2/8)	**14**/**04**/**2017** [day/month/year]
End date (3/8)	**14**/**04**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **150 mg** frequency: **once**
Route of administration (5/8)	**i.v.**
Indication (6/8)	Medical history: _____ or Adverse event: **Atrial fibrillation** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 21 (Concomitant Medication)

Medication (Trade name) (1/8)	**Baypress**
Start date (2/8)	**15**/**04**/**2017** [day/month/year]
End date (3/8)	**15**/**05**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **20 mg** frequency: **When required**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **Hypertensive crisis** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 22 (Concomitant Medication)

Medication (Trade name) (1/8)	**Nepresol (Dihydralazin)**
Start date (2/8)	**15**/**04**/**2017** [day/month/year]
End date (3/8)	**16**/**04**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **25 mg** frequency: **When required**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **Hypertensive crisis** or

	Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 23 (Concomitant Medication)

Medication (Trade name) (1/8)	**Nitrolingual**
Start date (2/8)	**15**/**04**/**2017** [day/month/year]
End date (3/8)	**16**/**04**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **1 ml** frequency: **When required**
Route of administration (5/8)	**sublingual spray**
Indication (6/8)	Medical history: _____ or Adverse event: **Hypertensive crisis** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 24 (Concomitant Medication)

Medication (Trade name) (1/8)	**Novalgin (Metamizol)**
Start date (2/8)	**04**/**04**/**2017** [day/month/year]
End date (3/8)	**10**/**04**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **3000 mg** frequency: **When required**
Route of administration (5/8)	**i.v.**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 25 (Concomitant Medication)

Medication (Trade name) (1/8)	**Humanalbumin**
Start date (2/8)	**11**/**04**/**2017** [day/month/year]
End date (3/8)	**18**/**04**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **20 g** frequency: **daily**
Route of administration (5/8)	**i.v.**
Indication (6/8)	Medical history: **immune complex glomerulonephritis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 26 (Concomitant Medication)

Medication (Trade name) (1/8)	**Fermed**
Start date (2/8)	**04**/**04**/**2017** [day/month/year]
End date (3/8)	**18**/**05**/**2017** [day/month/year] or _____
	total daily dose and unit: **100 mg**

Dose and frequency (4/8)	frequency: **3 times/week**
Route of administration (5/8)	**i.v.**
Indication (6/8)	Medical history: **immune complex glomerulonephritis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 27 (Concomitant Medication)

Medication (Trade name) (1/8)	**Trajenta**
Start date (2/8)	**08/04/2017** [day/month/year]
End date (3/8)	**17/06/2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **5 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Diabetes mellitus** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 28 (Concomitant Medication)

Medication (Trade name) (1/8)	**Trittico**
Start date (2/8)	**17/04/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **50 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Depressive episodes** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 29 (Concomitant Medication)

Medication (Trade name) (1/8)	**Dificlir**
Start date (2/8)	**26/04/2017** [day/month/year]
End date (3/8)	**05/05/2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **400 mg** frequency: **daily**
Route of administration (5/8)	**i.v.**
Indication (6/8)	Medical history: _____ or Adverse event: **C. difficile–associated diarrhea** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 30 (Concomitant Medication)

Medication (Trade name) (1/8)	**Pantoloc**

Start date (2/8)	**28/04/2017** [day/month/year]
End date (3/8)	**02/05/2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **40** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **Nausea** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 31 (Concomitant Medication)

Medication (Trade name) (1/8)	**Pantoloc**
Start date (2/8)	**03/05/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **20 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **Nausea** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 32 (Concomitant Medication)

Medication (Trade name) (1/8)	**Novalgin (Metamizol)**
Start date (2/8)	**10/04/2017** [day/month/year]
End date (3/8)	**08/07/2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **3000 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 33 (Concomitant Medication)

Medication (Trade name) (1/8)	**Sertralin**
Start date (2/8)	**26/04/2017** [day/month/year]
End date (3/8)	**05/07/2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **25 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Depressive episodes** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 34 (Concomitant Medication)

Medication (Trade name) (1/8)	**Sandimmun**

Start date (2/8)	**05**/**04**/**2017** [day/month/year]
End date (3/8)	**06**/**06**/**2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **100 mg** frequency: **1-0-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **kidney transplantation** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 35 (Concomitant Medication)

Medication (Trade name) (1/8)	**Baypress**
Start date (2/8)	**13**/**05**/**2017** [day/month/year]
End date (3/8)	**15**/**05**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **30 mg** frequency: **1-1-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hypertension** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 36 (Concomitant Medication)

Medication (Trade name) (1/8)	**Amlodipin**
Start date (2/8)	**18**/**05**/**2017** [day/month/year]
End date (3/8)	**17**/**06**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **10 mg** frequency: **0-0-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hypertension** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 37 (Concomitant Medication)

Medication (Trade name) (1/8)	**Tazonam**
Start date (2/8)	**28**/**04**/**2017** [day/month/year]
End date (3/8)	**29**/**05**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **9 g** frequency: **1-0-1**
Route of administration (5/8)	**i.v.**
Indication (6/8)	Medical history: _____ or Adverse event: **C. difficile–associated diarrhea** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	**Treatment for AE #5 and AE #7**

Instance-no: 38 (Concomitant Medication)

Medication (Trade name) (1/8)	**Hydal**
Start date (2/8)	**10**/**04**/**2017** [day/month/year]
End date (3/8)	**17**/**07**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **up to 7,8 mg** frequency: **up to 6 times/day when required**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 39 (Concomitant Medication)

Medication (Trade name) (1/8)	**Zofran**
Start date (2/8)	**13**/**04**/**2017** [day/month/year]
End date (3/8)	**16**/**04**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **8 mg** frequency: **1-0-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **Nausea** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 40 (Concomitant Medication)

Medication (Trade name) (1/8)	**Lovenox**
Start date (2/8)	**16**/**04**/**2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **40 mg** frequency: **daily**
Route of administration (5/8)	**s.c.**
Indication (6/8)	Medical history: _____ or Adverse event: _____ or Other: **Prophylaxis of thrombosis**
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 41 (Concomitant Medication)

Medication (Trade name) (1/8)	**Valcyte**
Start date (2/8)	**28**/**04**/**2017** [day/month/year]
End date (3/8)	**02**/**05**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **450 mg** frequency: **1-0-0**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **Cytomegalovirus infection** or Other: _____
Was the medication administered to treat pain (7/8)	**no**

Comments (8/8)	_____ _____ _____

Instance-no: 42 (Concomitant Medication)

Medication (Trade name) (1/8)	**Baypress**
Start date (2/8)	**21/04/2017** [day/month/year]
End date (3/8)	**25/04/2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **40 mg** frequency: **1-1-1-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hypertension** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 43 (Concomitant Medication)

Medication (Trade name) (1/8)	**Konakion**
Start date (2/8)	**29/04/2017** [day/month/year]
End date (3/8)	**02/05/2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **10 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 44 (Concomitant Medication)

Medication (Trade name) (1/8)	**Paspertin**
Start date (2/8)	**13/05/2017** [day/month/year]
End date (3/8)	**18/05/2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **30 mg** frequency: **1-1-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **Nausea** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 45 (Concomitant Medication)

Medication (Trade name) (1/8)	**Humanalbumin**
Start date (2/8)	**19/06/2017** [day/month/year]
End date (3/8)	**21/06/2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **40 g** frequency: **daily**
Route of administration (5/8)	**i.v.**
	Medical history: _____ or

Indication (6/8)	Adverse event: **suspected drug induced liver injury** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 46 (Concomitant Medication)

Medication (Trade name) (1/8)	**Ursofalk**
Start date (2/8)	**13**/**07**/**2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **500 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **Drug induced liver injury** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 47 (Concomitant Medication)

Medication (Trade name) (1/8)	**Paspertin**
Start date (2/8)	**12**/**06**/**2017** [day/month/year]
End date (3/8)	**14**/**07**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **30 mg** frequency: **1-1-1 10 mg**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **Vomiting** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 48 (Concomitant Medication)

Medication (Trade name) (1/8)	**Ondansan**
Start date (2/8)	**19**/**06**/**2017** [day/month/year]
End date (3/8)	**25**/**07**/**2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **12 mg** frequency: **1-1-1 4 mg**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **Vomiting** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 49 (Concomitant Medication)

Medication (Trade name) (1/8)	**Molaxole**
Start date (2/8)	**01**/**07**/**2017** [day/month/year]
End date (3/8)	**03**/**07**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **1 package** frequency: **daily**

Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **suspected drug induced liver injury** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 50 (Concomitant Medication)

Medication (Trade name) (1/8)	**Teicoplanin**
Start date (2/8)	**27**/**06**/**2017** [day/month/year]
End date (3/8)	**06**/**07**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **dependent on trough level (600 - 1600 mg)** frequency: **daily**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: _____ or Adverse event: **Infection of unknown origin** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 51 (Concomitant Medication)

Medication (Trade name) (1/8)	**Fosfomycin**
Start date (2/8)	**28**/**06**/**2017** [day/month/year]
End date (3/8)	**09**/**07**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **8 g** frequency: **2x 4 g daily**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: _____ or Adverse event: **Infection of unknown origin** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 52 (Concomitant Medication)

Medication (Trade name) (1/8)	**Xanor (Alprazolam)**
Start date (2/8)	**14**/**07**/**2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **0,25 mg** frequency: **daily**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Depressive episodes** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 53 (Concomitant Medication)

Medication (Trade name) (1/8)	**Aranesp**
Start date (2/8)	**11**/**04**/**2017** [day/month/year]

End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **150 µg once a week** frequency: **once a week**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: **immune complex glomerulonephritis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 54 (Concomitant Medication)

Medication (Trade name) (1/8)	**Sandimmun**
Start date (2/8)	**06**/**06**/**2017** [day/month/year]
End date (3/8)	**20**/**06**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **50 mg** frequency: **1-0-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **kidney transplantation** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 55 (Concomitant Medication)

Medication (Trade name) (1/8)	**Hydal**
Start date (2/8)	**28**/**05**/**2017** [day/month/year]
End date (3/8)	**06**/**06**/**2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **8 mg** frequency: **1-0-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 56 (Concomitant Medication)

Medication (Trade name) (1/8)	**Hydal**
Start date (2/8)	**06**/**06**/**2017** [day/month/year]
End date (3/8)	**09**/**07**/**2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **16 mg** frequency: **1-0-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 57 (Concomitant Medication)

Medication (Trade name) (1/8)	**Hydal**
Start date (2/8)	**09/07/2017** [day/month/year]
End date (3/8)	**17/07/2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **4 mg** frequency: **1-0-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 58 (Concomitant Medication)

Medication (Trade name) (1/8)	**Ondansan**
Start date (2/8)	**25/07/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **4 mg** frequency: **1x day**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: **Vomiting** or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 59 (Concomitant Medication)

Medication (Trade name) (1/8)	**Novalgin (Metamizol)**
Start date (2/8)	**08/07/2017** [day/month/year]
End date (3/8)	**19/07/2017** [day/month/year] or **dosage changed**
Dose and frequency (4/8)	total daily dose and unit: **1500 mg** frequency: **1-1-1**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 60 (Concomitant Medication)

Medication (Trade name) (1/8)	**Novalgin (Metamizol)**
Start date (2/8)	**19/07/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **500 mg** frequency: **1x day**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Calciphylaxis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
	_____

Comments (8/8)	_____ _____

Instance-no: 61 (Concomitant Medication)

Medication (Trade name) (1/8)	**Humanalbumin**
Start date (2/8)	**29**/**05**/**2017** [day/month/year]
End date (3/8)	**30**/**05**/**2017** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **40 g** frequency: **1-0-1**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: **immune complex glomerulonephritis** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 62 (Concomitant Medication)

Medication (Trade name) (1/8)	**Sertralin**
Start date (2/8)	**05**/**07**/**2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **50 mg** frequency: **1x day**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Depressive episodes** or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 63 (Concomitant Medication)

Medication (Trade name) (1/8)	_____
Start date (2/8)	__/__/____ [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: _____ frequency: _____
Route of administration (5/8)	_____
Indication (6/8)	Medical history: _____ or Adverse event: _____ or Other: _____
Was the medication administered to treat pain (7/8)	___
Comments (8/8)	_____ _____ _____

Adverse event [CRF-page 16/17] - Table

Instance-no: 1 (Adverse Event)

Adverse event (1/9)	**Nausea**
Start date (2/9)	**09**/**04**/20**17** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**unlikely**

Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	[ ] None **[x] Drug treatment** [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Not recovered/not resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: __/__/20__ [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 2 (Adverse Event)

Adverse event (1/9)	**Hypotension**
Start date (2/9)	**12**/**04**/20**17** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**not related**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	[ ] None [ ] Drug treatment **[x] Other** if other - please specify: **No Hemodialysis**
Outcome (8/9)	**Recovered/resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **13**/**04**/20**17** [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 3 (Adverse Event)

Adverse event (1/9)	**Atrial fibrillation**
Start date (2/9)	**14**/**04**/20**17** [day/month/year]
Severity (3/9)	**moderate**
Causal relationship to study treatment (4/9)	**unlikely**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
	[ ] None **[x] Drug treatment** [ ] Other if other - please specify:

Countermeasures (7/9)	_____ _____ _____
Outcome (8/9)	**Recovered / resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **14**/**04**/20**17** [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 4 (Adverse Event)

Adverse event (1/9)	**Hypertensive crisis**
Start date (2/9)	**15**/**04**/20**17** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**unlikely**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	[ ] None **[x] Drug treatment** [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Recovered / resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **16**/**04**/20**17** [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 5 (Adverse Event)

Adverse event (1/9)	**C. difficile–associated diarrhea**
Start date (2/9)	**24**/**04**/20**17** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**not related**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	[ ] None **[x] Drug treatment** [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Recovered / resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **05**/**05**/20**17** [day/month/year]
Comments (9/9)	_____ _____

	_____

Instance-no: 6 (Adverse Event)

Adverse event (1/9)	**C. difficile infection**
Start date (2/9)	**22**/**05**/20**17** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**not related**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	**[x] None** [ ] Drug treatment [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Recovered/resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **19**/**07**/20**17** [day/month/year]
Comments (9/9)	**positiv test. asymptomatic, no treatment started.**

Instance-no: 7 (Adverse Event)

Adverse event (1/9)	**Calciphylaxis related necrosis**
Start date (2/9)	**10**/**05**/20**17** [day/month/year]
Severity (3/9)	**moderate**
Causal relationship to study treatment (4/9)	**unlikely**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	[ ] None [ ] Drug treatment **[x] Other** if other - please specify: **Debridement**
Outcome (8/9)	**Not recovered/not resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: __/__/20__ [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 8 (Adverse Event)

Adverse event (1/9)	**Vomiting**
Start date (2/9)	**12**/**04**/20**17** [day/month/year]
Severity (3/9)	**moderate**
Causal relationship to study treatment (4/9)	**probable**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization

	[ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Drug withdrawn**
Countermeasures (7/9)	[ ] None **[x] Drug treatment** [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Not recovered/not resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: __/__/20__ [day/month/year]
Comments (9/9)	**After decreasing the IP without improvement, the IP was withdrawn at June 26th.**

Instance-no: 9 (Adverse Event)

Adverse event (1/9)	**Cholestasis**
Start date (2/9)	**09**/**06**/20**17** [day/month/year]
Severity (3/9)	**moderate**
Causal relationship to study treatment (4/9)	**unlikely**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose reduced**
Countermeasures (7/9)	[ ] None [ ] Drug treatment **[x] Other** if other - please specify: **Termination of drugs**
Outcome (8/9)	**Not recovered/not resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: __/__/20__ [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 10 (Adverse Event)

Adverse event (1/9)	**Drug induced liver injury**
Start date (2/9)	**10**/**07**/20**17** [day/month/year]
Severity (3/9)	**severe**
Causal relationship to study treatment (4/9)	**unlikely**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Not applicable**
Countermeasures (7/9)	[ ] None [ ] Drug treatment **[x] Other** if other - please specify: **All drugs which are not necessarly needed are withdrawn**
Outcome (8/9)	**Not recovered/not resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: __/__/20__ [day/month/year]
Comments (9/9)	**At this point of time the study IMP was on pause.**

Instance-no: 11 (Adverse Event)

Adverse event (1/9)	**suspected drug induced liver injury**
Start date (2/9)	**13**/**06**/20**17** [day/month/year]
Severity (3/9)	**severe**
Causal relationship to study treatment (4/9)	**unlikely**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose reduced**
Countermeasures (7/9)	[ ] None [ ] Drug treatment **[x] Other** if other - please specify: **Termination of other oral and i.v. drugs**
Outcome (8/9)	**Recovered / resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **10**/**07**/20**17** [day/month/year]
Comments (9/9)	**IMP was reduced on 19th of June 2017. Suspected drug induced liver injury was proven by biopsy on 10th of July**

Instance-no: 12 (Adverse Event)

Adverse event (1/9)	**undulating vomiting**
Start date (2/9)	**11**/**07**/20**17** [day/month/year]
Severity (3/9)	**severe**
Causal relationship to study treatment (4/9)	**possible**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Drug withdrawn**
Countermeasures (7/9)	[ ] None **[x] Drug treatment** [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Not recovered / not resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: __/__/20__ [day/month/year]
Comments (9/9)	**ongoing at final examination.**

Instance-no: 13 (Adverse Event)

Adverse event (1/9)	**Infection of unknown origin**
Start date (2/9)	**28**/**06**/20**17** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**not related**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant

Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	[ ] None **[x] Drug treatment** [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Recovered/resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **09**/**07**/20**17** [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 14 (Adverse Event)

Adverse event (1/9)	**Cytomegalovirus infection**
Start date (2/9)	**28**/**04**/20**17** [day/month/year]
Severity (3/9)	**mild**
Causal relationship to study treatment (4/9)	**not related**
Serious adverse event (5/9)	**no** if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	**Dose not changed**
Countermeasures (7/9)	[ ] None **[x] Drug treatment** [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	**Recovered/resolved** if recovered/resolved or recovered/resolved with sequelae - please provide stop date: **02**/**05**/20**17** [day/month/year]
Comments (9/9)	_____ _____ _____

Instance-no: 15 (Adverse Event)

Adverse event (1/9)	_____
Start date (2/9)	__/__/20__ [day/month/year]
Severity (3/9)	_____
Causal relationship to study treatment (4/9)	_____
Serious adverse event (5/9)	___ if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	_____
Countermeasures (7/9)	[ ] None [ ] Drug treatment [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	_____ if recovered/resolved or recovered/resolved with sequelae - please provide stop date:

	__/__/20__ [day/month/year]
Comments (9/9)	_____ _____ _____

Concomitant procedure/measure [CRF-page 17/17] - Table	
Instance-no: 1 (Concomitant Procedure/Measure)	
Procedure (1/5)	**Hemodialysis**
Start date (2/5)	**04/04/2017** [day/month/year]
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Indication (4/5)	Medical history/concomitant disease: **Renal transplant failure** or Adverse event: _____ or Other: _____
Comments (5/5)	_____ _____ _____
Instance-no: 2 (Concomitant Procedure/Measure)	
Procedure (1/5)	**Debridement**
Start date (2/5)	**10/05/2017** [day/month/year]
End date (3/5)	**10/05/2017** [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: _____ or Adverse event: **Calciphylaxis related necrosis** or Other: _____
Comments (5/5)	_____ _____ _____
Instance-no: 3 (Concomitant Procedure/Measure)	
Procedure (1/5)	**Debridement**
Start date (2/5)	**16/05/2017** [day/month/year]
End date (3/5)	**16/05/2017** [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: _____ or Adverse event: **Calciphylaxis related necrosis** or Other: _____
Comments (5/5)	_____ _____ _____
Instance-no: 4 (Concomitant Procedure/Measure)	
Procedure (1/5)	**Debridement**
Start date (2/5)	**02/06/2017** [day/month/year]
End date (3/5)	**02/06/2017** [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: _____ or Adverse event: **Calciphylaxis related necrosis** or Other: _____
Comments (5/5)	_____ _____ _____
Instance-no: 5 (Concomitant Procedure/Measure)	
Procedure (1/5)	**split skin graft**
Start date (2/5)	**02/06/2017** [day/month/year]
End date (3/5)	**02/06/2017** [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: _____ or Adverse event: **Calciphylaxis related necrosis** or Other: _____
Comments (5/5)	_____ _____ _____
Instance-no: 6 (Concomitant Procedure/Measure)	
Procedure (1/5)	**Debridement**

Start date (2/5)	**23**/**05**/**2017** [day/month/year]
End date (3/5)	**23**/**05**/**2017** [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: _____ or Adverse event: **Calciphylaxis related necrosis** or Other: _____
Comments (5/5)	_____ _____ _____

Instance-no: 7 (Concomitant Procedure/Measure)

Procedure (1/5)	**split skin graft**
Start date (2/5)	**23**/**06**/**2017** [day/month/year]
End date (3/5)	**23**/**06**/**2017** [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: _____ or Adverse event: **Calciphylaxis related necrosis** or Other: _____
Comments (5/5)	_____ _____ _____

Instance-no: 8 (Concomitant Procedure/Measure)

Procedure (1/5)	**Liver biopsy**
Start date (2/5)	**10**/**07**/**2017** [day/month/year]
End date (3/5)	**10**/**07**/**2017** [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: _____ or Adverse event: **suspected drug induced liver injury** or Other: _____
Comments (5/5)	_____ _____ _____

Instance-no: 9 (Concomitant Procedure/Measure)

Procedure (1/5)	_____
Start date (2/5)	__/__/____ [day/month/year]
End date (3/5)	__/__/____ [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: _____ or Adverse event: _____ or Other: _____
Comments (5/5)	_____ _____ _____

I confirm that I have carefully examined all entries of this patient. All information entered by myself or my colleagues is, to the best of my knowledge, correct as of the date below

Date: _____

Signature and stamp of investigator: _____

Study STS-CSM-1/13, Center: Medical University of Vienna [0103]
Patient No. 2: CRF Hardcopy, 18.09.2018 , 13:00:21

Screening/Start of run-in phase [17.01.2018]

Demographic information [CRF-page 1/15]	
Date of written informed consent (1/5)	**17**/**01**/20**18** [day/month/year]
Patient ID (2/5)	**01**-**03**-**002** (country-site-patient)
Patient year of birth (3/5)	19**88** [year] Age (at date of informed consent): **29** years
Gender (4/5)	**female**
Race of patient (5/5)	**asiatic** if other - please specify: _____ _____ _____

Inclusion/exclusion criteria [CRF-page 2/15]	
Inclusion criteria	
Patient ⩾ 18 years (1/11)	**yes**
Male or female HD patients with a diagnosis of calciphylaxis (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching) (2/11)	**yes**
Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study (3/11)	**yes**
Exclusion criteria	
Females who are pregnant (positive pregnancy test at screening or during study phase) or lactating. If having reproductive potential are considered potentially ineligible with respect to use highly effective methods of birth control throughout the study. (4/11)	**no**
Patients who have participated in any other investigational studies within 30 days previous to enrollment (5/11)	**no**
History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment (6/11)	**no**
Good response to conventional treatment (7/11)	**no**
Life expectancy less than 4 months in the judgement of the investigator (8/11)	**no**
Comments (9/11)	_____ _____ _____

Clinical examination [CRF-page 3/15]	
Vital signs	
Date of assessment (1/24)	**17**/**01**/20**18** [day/month/year]
Body height (2/24)	**156** cm
Body weight (3/24)	**92** kg
Blood pressure (measured after patient has rested for 5 minutes) (4/24)	**132** mmHg / **92** mmHg [systolic/diastolic]
Heart rate (measured after patient has rested for 5 minutes) (5/24)	**97** b/min
BMI (calculated) (6/24)	**37.8** kg/m²
12-lead ECG	
ECG findings (7/24)	Date: **17**/**01**/20**18** [day/month/year] Result: **normal** if abnormal and clinically relevant - please specify: _____ _____ _____

Physical examination	
Were physical examinations performed (8/24)	**yes** if yes - date: **17**/**01**/20**18** [day/month/year]
Head (9/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (10/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (11/24)	**abnormal** if abnormal - please specify: **Systolicum at aortical valve and Erb** if abnormal - clinically relevant: **no**
Dermatological (12/24)	**abnormal** if abnormal - please specify: **Lesion lower limb** if abnormal - clinically relevant: **yes**
Musculosceletal (13/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (14/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (15/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Neurological (16/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Other (17/24)	**not done** if normal or abnormal - please specify: _____ _____ _____

	if abnormal - clinically relevant: ___
Calciphylaxis diagnosis	
Calciphylaxis diagnosed according to typical signs and symptoms (18/24)	**yes** if yes - please check all that apply: **[x] Severe pain** **[x] Livedo** **[x] Violaceous plaques** [ ] Ulcerations **[x] Necroses** if ulcerations and/or necroses - have other causes been excluded: **no**
Tobacco use	
Tobacco use (19/24)	**Non-smoker**
Checklist	
Does the patient have any relevant medical history or concomitant diseases (20/24)	**yes**
Does the patient receive any concomitant medication (including pain medication) (21/24)	**yes**
Any concomitant procedures/measures performed (22/24)	**yes**
Has sample for biobanking been taken (23/24)	**yes** if yes - date: **17**/**01**/20**18** [day/month/year]
Comments (24/24)	_____ _____ _____

Hematology and venous blood gas analysis [CRF-page 4/15]	
Hematology	
Date of sample (1/12)	**17**/**01**/20**18** [day/month/year]
Patient's age at sampling date (2/12)	**[x] same as at informed consent** (**29** years) or ___ years
Hemoglobin (3/12)	**7.3 g/dl** if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **medical history**
White blood cells (4/12)	**17.92 G/l** if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **medical history**
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min **[x] not available**
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	**29.5 mmHg** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Bicarbonate (8/12)	**24.4 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (9/12)	_____ _____ _____
Comments (10/12)	_____ _____ _____

Clinical chemistry [CRF-page 5/15]

Clinical Chemistry	
Date of sample (1/25)	**17**/**01**/20**18** [day/month/year]
Patient's age at sampling date (2/25)	**[x] same as at informed consent** (**29** years) or ___ years
IPTH (3/25)	**477 pg/ml** if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **medical history**
Calcium (4/25)	**2.22 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Phosphate (5/25)	**1.13 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Alk. phosphatase (6/25)	**401 U/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
pH serum (7/25)	**7.4 1/1** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	**18.9 mg/dl** if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
Creatinine (9/25)	**4.66 mg/dl** if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **underlying disease**
Albumin (10/25)	**22.5 g/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Sodium (11/25)	**139 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Potassium (12/25)	**4.29 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Chloride (13/25)	**99 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Magnesium (14/25)	**0.82 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GOT (AST) (15/25)	**21 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
GPT (ALT) (16/25)	**24 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Gamma-GT (17/25)	**443 U/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
	24 U/l

Amylase (18/25)	if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Lipase (19/25)	**23 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Urea (20/25)	**15.7 mg/dl** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Uric acid (21/25)	**3.3 mg/dl** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	**5 pg/ml** if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **medical history**
25-Hydroxy-Vitamin D (23/25)	**12.4 nmol/l** if outside normal limits - clinically relevant ? **yes** if clinically relevant - causal relationship with: **medical history**
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____

Wound, pain and other assessments [CRF-page 6/15]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/4)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/4)	**yes** if yes - degree of pain: **80** mm
Pregnancy test	
Pregnancy test (3/4)	**negative** Date:**19**/**01**/20**18** [day/month/year]
Comments (4/4)	_____ _____ _____

End of run-in phase

Inclusion/exclusion criteria [CRF-page 7/15]	
Inclusion criteria	
Patient $\geqslant$ 18 years (1/11)	**yes**
Male or female HD patients with a diagnosis of calciphylaxis. (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching). (2/11)	**yes**
Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study (3/11)	**yes**
Exclusion criteria	
Females who are pregnant (positive pregnancy test at screening or during study phase) or lactating. If having reproductive potential are considered potentially ineligible with respect to use highly effective methods of birth control throughout the study. (4/11)	**no**
Patients who have participated in any other investigational studies within 30 days previous to enrollment (5/11)	**no**
History of alcohol abuse, illicit drug use, significant mental illness,	

physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment (6/11)	**no**
Good response to conventional treatment (7/11)	**yes**
Life expectancy less than 4 months in the judgement of the investigator (8/11)	**yes**
Comments (9/11)	_____ _____ _____

Completion of run-in-phase [CRF-page 8/15]	
Biopsy report of consisting wound available (1/7)	**yes** if yes: please check all that apply: **[x] none** [ ] diagnosis of calciphylaxis confirmed [ ] other causes for necroses and ulcerations excluded
Has a skin biopsy been taken (2/7)	**no** if yes, date:__/__/20__ [day/month/year] if yes - calciphylaxis diagnosis confirmed by analysis: ___
Has the patient agreed to participate in the clinical trial and to undergo STS treatment (3/7)	**yes**
Disease status under BSC (4/7)	**initially stable disease**
Have all screening/baseline assessments been performed and is patient considered eligible for treatment start (5/7)	**no** if no - please check all that apply: **[x] patient did not meet all in-/exclusion criteria** [ ] withdrawal of informed consent by the patient [ ] discretion of the investigator **[x] calciphylaxis diagnosis not confirmed** [ ] other reason if other reason - please specify: _____ _____ _____
Has all patient data been entered as far as possible and checked, all data can be set read-only (6/7)	**yes**
Comments (7/7)	_____ _____ _____

Lesions

Lesions [CRF-page 9/15] - Table	
Instance-no: 1 (Lesions)	
Lesion (1/25)	Lesion number: **1** Lesion location: **lateral right lower limb**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	**01**/**02**/20**18** [day/month/year] or [ ] still present
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **17**/**01**/20**18** [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **2.2** cm^2 or [ ] Wound area not assessed Size: **2** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type:

	4 Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **2** Total score: **24**
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **2** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **0** Total score: **22**
Photodocumentation V0 (7/25)	Date: **01**/**02**/20**18** [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _

	Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V2 (10/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability:

	_ Total score: __
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**

Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size:

Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	_ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	**Wound assessment and revPWAT V0 not done**
Instance-no: 2 (Lesions)	
Lesion (1/25)	Lesion number: **2** Lesion location: **dorsal right lower limb**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	__/__/20__ [day/month/year] or **[x] still present**
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **17**/**01**/20**18** [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **4.5** cm^2 or [ ] Wound area not assessed Size: **2** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **2** Total score: **24**
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **2** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **0**

	Total score: **22**
Photodocumentation V0 (7/25)	Date: **01**/**02**/20**18** [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: ___**.**__ cm^2 or **[x] Wound area not assessed** Size: _ Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **3** Periulcer skin viability: **2** Total score: **24**
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **1** cm^2 or [ ] Wound area not assessed Size: **1** Depth: **2** Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **4** Total amount of granulation tissue: **0** Edges: **0** Periulcer skin viability: **1** Total score: **8**
Photodocumentation V2 (10/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___**.**__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name]

Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size:

Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	_ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type:

Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	_ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	**At Wound assessment and revPWAT V0 total wound area not done by M. L.**

Instance-no: 3 (Lesions)

Lesion (1/25)	Lesion number: **3** Lesion location: **medial right lower limb**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	**01**/**02**/20**18** [day/month/year] or [ ] still present
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **17**/**01**/20**18** [day/month/year] or _____

Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **2.9** cm^2 or [ ] Wound area not assessed Size: **2** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **3** Total score: **25**
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **26.5** cm^2 or [ ] Wound area not assessed Size: **4** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **1** Total score: **25**
Photodocumentation V0 (7/25)	Date: **01**/**02**/20**18** [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed**

Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Size: **3** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **3** Periulcer skin viability: **1** Total score: **25**
Photodocumentation V2 (10/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth:

Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	_ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue:

(Dermatologist 2) (18/25)	_ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _

	Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	**Wound assessment and revPWAT V0 not done by Dermatologist ... L.**
Instance-no: 4 (Lesions)	
Lesion (1/25)	Lesion number: **4** Lesion location: **frontal right lower limb**
Date of occurrence (2/25)	__/__/20__ [day/month/year] or **[x] before study start**
Date of healing (3/25)	__/__/20__ [day/month/year] or **[x] still present**
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: **17**/**01**/20**18** [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: **18** cm^2 or [ ] Wound area not assessed Size: **3** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **3** Periulcer skin viability: **3** Total score: **27**
	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: **19** cm^2 or [ ] Wound area not assessed Size: **3** Depth: **2**

Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Necrotic tissue type: **0** Total amount of necrotic tissue: **0** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **2** Periulcer skin viability: **1** Total score: **16**
Photodocumentation V0 (7/25)	Date: **01**/**02**/20**18** [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: **M** / **L** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: _ Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **3** Periulcer skin viability: **2** Total score: **23**
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: **J** / **K** [first/last name] Total wound area: ___.__ cm^2 or **[x] Wound area not assessed** Size: **3** Depth: **2** Necrotic tissue type: **4** Total amount of necrotic tissue: **4** Granulation tissue type: **4** Total amount of granulation tissue: **4** Edges: **3** Periulcer skin viability: **2** Total score: **26**
Photodocumentation V2 (10/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _

Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _

	Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges:

	_ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or **no photodocumentation done**
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _

	Total score: __
Comments (25/25)	**At Wound assessment and revPWAT V0 total wound area not done by M. L.**
Instance-no: 5 (Lesions)	
Lesion (1/25)	Lesion number: __ Lesion location: _____
Date of occurrence (2/25)	__/__/20__ [day/month/year] or [ ] before study start
Date of healing (3/25)	__/__/20__ [day/month/year] or [ ] still present
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V0 (7/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _

	Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V2 (10/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue:

	_ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _

	Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability:

	_ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	_____ _____ _____

Follow-up telephone interviews

Follow-up telephone interviews [CRF-page 10/15] - Table	
Instance-no: 1 (Follow-up telephone interviews)	
Follow-up telephone interview 1 Patient status [Instance-no: 1, page 1/1]	
Date of telephone call (1/7)	__/__/20__ [day/month/year]
Survival status	
Patient alive (2/7)	___
Disease status	
Is the disease still present (3/7)	___
Continuation STS-treatment	
Has the patient received further STS-treatment since last visit (4/7)	___
Further treatment	

Any further or additional treatment (5/7)	___
New calciphylaxis medication	
Any new medication for treatment of calciphylaxis (6/7)	___
Comments (7/7)	_____ _____ _____

End of study [08.02.2018]

End of study [CRF-page 11/15]	
Date of study end (1/6)	**08**/**02**/20**18** [day/month/year]
Has the patient been listed on a transplant waiting list (2/6)	**no** if yes, date: __/__/20__ [day/month/year]
Date of last contact when patient was alive (3/6)	**26**/**02**/20**18** [day/month/year]
Reason of study end (4/6)	**screening failure** if early discontinuation, lost to follow-up or other - please specify: _____ _____ _____ if patient died - date of death: __/__/20__ [day/month/year] [ ] not available reason of death: _____ if other reason - please specify: _____ _____ _____
Has all patient data been entered as far as possible and checked, all data can be set read-only (5/6)	**yes**
Comments (6/6)	_____ _____ _____

Medical history, concomitant medication and procedures, adverse events

Medical history [CRF-page 12/15] - Table	
Instance-no: 1 (Medical History)	
Condition (1/5)	**Diabetes mellitus**
Start date (2/5)	**05**/**07**/**2010** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____
Instance-no: 2 (Medical History)	
Condition (1/5)	**Chronic Kidney Disease**
Start date (2/5)	**22**/**11**/**2014** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____
Instance-no: 3 (Medical History)	
Condition (1/5)	**Diabetic neuropathy**
Start date (2/5)	**22**/**11**/**2014** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____
Instance-no: 4 (Medical History)	

Condition (1/5)	**Diabetic retinopathy**
Start date (2/5)	**05/07/2010** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____

Instance-no: 5 (Medical History)

Condition (1/5)	**Cataract**
Start date (2/5)	__/__/____ [day/month/year] or **[x] unknown**
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____

Instance-no: 6 (Medical History)

Condition (1/5)	**Adipositas**
Start date (2/5)	__/__/____ [day/month/year] or **[x] unknown**
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____

Instance-no: 7 (Medical History)

Condition (1/5)	**Hypertension**
Start date (2/5)	**05/07/2010** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 8 (Medical History)

Condition (1/5)	**Peripheral artery disease**
Start date (2/5)	**28/12/2017** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 9 (Medical History)

Condition (1/5)	**Hyperparathyroidism**
Start date (2/5)	__/__/____ [day/month/year] or **[x] unknown**
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 10 (Medical History)

Condition (1/5)	**Renal Anaemia**
Start date (2/5)	__/__/____ [day/month/year] or **[x] unknown**
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 11 (Medical History)

Condition (1/5)	**Soft tissue infection**

Start date (2/5)	**22**/**12**/**2017** [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Treated with medications at study start (4/5)	**yes**
Comments (5/5)	_____ _____ _____

Instance-no: 12 (Medical History)

Condition (1/5)	**Calciphylaxis**
Start date (2/5)	**08**/**01**/**2018** [day/month/year] or [ ] unknown
End date (3/5)	**08**/**02**/**2018** [day/month/year] or _____
Treated with medications at study start (4/5)	**no**
Comments (5/5)	_____ _____ _____

Instance-no: 13 (Medical History)

Condition (1/5)	_____
Start date (2/5)	__/__/____ [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or _____
Treated with medications at study start (4/5)	___
Comments (5/5)	_____ _____ _____

Concomitant medication [CRF-page 13/15] - Table

Instance-no: 1 (Concomitant Medication)

Medication (Trade name) (1/8)	**Mimpara**
Start date (2/8)	**18**/**01**/**2018** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **30 mg** frequency: **1x day**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hyperparathyroidism** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 2 (Concomitant Medication)

Medication (Trade name) (1/8)	**Acemin (Lisinopril)**
Start date (2/8)	**20**/**11**/**2014** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **40 mg** frequency: **2x 20 mg**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hypertension** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____

	_____

Instance-no: 3 (Concomitant Medication)

Medication (Trade name) (1/8)	**Thrombo-ASS**
Start date (2/8)	**30/12/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **100 mg** frequency: **1x day**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Peripheral artery disease** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 4 (Concomitant Medication)

Medication (Trade name) (1/8)	**Pantoloc**
Start date (2/8)	**31/12/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **40 mg** frequency: **1x day**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: _____ or Adverse event: (not available) or Other: **Prophylaxis**
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 5 (Concomitant Medication)

Medication (Trade name) (1/8)	**Concor**
Start date (2/8)	**04/08/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **10 mg** frequency: **2x 5 mg**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hypertension** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 6 (Concomitant Medication)

Medication (Trade name) (1/8)	**Galvus**
Start date (2/8)	**04/08/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **50 mg** frequency: **1x day**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Diabetes mellitus** or Adverse event: (not available) or Other: _____

Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 7 (Concomitant Medication)

Medication (Trade name) (1/8)	**Renvela**
Start date (2/8)	**04/08/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **4800 mg** frequency: **3x 1600 mg**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Chronic Kidney Disease** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 8 (Concomitant Medication)

Medication (Trade name) (1/8)	**Gabapentin**
Start date (2/8)	**20/07/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **100 mg** frequency: **1x day**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Diabetic neuropathy** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 9 (Concomitant Medication)

Medication (Trade name) (1/8)	**Doxazosin**
Start date (2/8)	**04/08/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **6 mg** frequency: **4 mg - 0- 2 mg**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hypertension** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 10 (Concomitant Medication)

Medication (Trade name) (1/8)	**Spirono**
Start date (2/8)	**04/08/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **25 mg** frequency: **1x day**

Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Hypertension** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 11 (Concomitant Medication)

Medication (Trade name) (1/8)	**Novalgin (Metamizol)**
Start date (2/8)	**28/12/2017** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **3000 mg** frequency: **3x 1000 mg**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Peripheral artery disease** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 12 (Concomitant Medication)

Medication (Trade name) (1/8)	**Aranesp**
Start date (2/8)	**04/08/2014** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **100 mg weekly** frequency: **1x/ week**
Route of administration (5/8)	**sub cutanous**
Indication (6/8)	Medical history: **Renal Anaemia** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 13 (Concomitant Medication)

Medication (Trade name) (1/8)	**Hydal**
Start date (2/8)	**09/01/2018** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **8 mg** frequency: **2x 4 mg**
Route of administration (5/8)	**oral**
Indication (6/8)	Medical history: **Peripheral artery disease** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**yes**
Comments (8/8)	_____ _____ _____

Instance-no: 14 (Concomitant Medication)

Medication (Trade name) (1/8)	**Lovenox**
Start date (2/8)	**14/01/2018** [day/month/year]

End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **120 mg** frequency: **2x 60 mg**
Route of administration (5/8)	**sub cutanous**
Indication (6/8)	Medical history: **Peripheral artery disease** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 15 (Concomitant Medication)

Medication (Trade name) (1/8)	**Levemir**
Start date (2/8)	**13/04/2016** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **26 IE** frequency: **12- 0 -14**
Route of administration (5/8)	**sub cutanous**
Indication (6/8)	Medical history: **Diabetes mellitus** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 16 (Concomitant Medication)

Medication (Trade name) (1/8)	**Novorapid**
Start date (2/8)	**15/11/2010** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **dependent on serum glucose** frequency: **daily**
Route of administration (5/8)	**sub cutanous**
Indication (6/8)	Medical history: **Diabetes mellitus** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 17 (Concomitant Medication)

Medication (Trade name) (1/8)	**Pridax**
Start date (2/8)	**08/01/2018** [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or **ongoing after final examination**
Dose and frequency (4/8)	total daily dose and unit: **40 mcg** frequency: **1x day**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: **Peripheral artery disease** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 18 (Concomitant Medication)	
Medication (Trade name) (1/8)	**Dalacin**
Start date (2/8)	**17**/**01**/**2018** [day/month/year]
End date (3/8)	**02**/**02**/**2018** [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: **1800 mg** frequency: **3x 600 mg**
Route of administration (5/8)	**intravenous**
Indication (6/8)	Medical history: **Soft tissue infection** or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	**no**
Comments (8/8)	_____ _____ _____

Instance-no: 19 (Concomitant Medication)	
Medication (Trade name) (1/8)	_____
Start date (2/8)	__/__/____ [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: _____ frequency: _____
Route of administration (5/8)	_____
Indication (6/8)	Medical history: _____ or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	___
Comments (8/8)	_____ _____ _____

Adverse event [CRF-page 14/15] - Table	
Instance-no: 1 (Adverse Event)	
Adverse event (1/9)	_____
Start date (2/9)	__/__/20__ [day/month/year]
Severity (3/9)	_____
Causal relationship to study treatment (4/9)	_____
Serious adverse event (5/9)	___ if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	_____
Countermeasures (7/9)	[ ] None [ ] Drug treatment [ ] Other if other - please specify: _____ _____ _____
Outcome (8/9)	_____ if recovered/resolved or recovered/resolved with sequelae - please provide stop date: __/__/20__ [day/month/year]
Comments (9/9)	_____ _____

	_____

Concomitant procedure/measure [CRF-page 15/15] - Table	
Instance-no: 1 (Concomitant Procedure/Measure)	
Procedure (1/5)	**Haemodialysis**
Start date (2/5)	**29/12/2017** [day/month/year]
End date (3/5)	__/__/____ [day/month/year] or **ongoing after final examination**
Indication (4/5)	Medical history/concomitant disease: **Chronic Kidney Disease** or Adverse event: (not available) or Other: _____
Comments (5/5)	_____ _____ _____
Instance-no: 2 (Concomitant Procedure/Measure)	
Procedure (1/5)	**Percutaneous transluminal angioplasty**
Start date (2/5)	**29/01/2018** [day/month/year]
End date (3/5)	**29/01/2018** [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: **Peripheral artery disease** or Adverse event: (not available) or Other: _____
Comments (5/5)	_____ _____ _____
Instance-no: 3 (Concomitant Procedure/Measure)	
Procedure (1/5)	_____
Start date (2/5)	__/__/____ [day/month/year]
End date (3/5)	__/__/____ [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: _____ or Adverse event: (not available) or Other: _____
Comments (5/5)	_____ _____ _____

I confirm that I have carefully examined all entries of this patient. All information entered by myself or my colleagues is, to the best of my knowledge, correct as of the date below

Date: _____

Signature and stamp of investigator: _____

Study STS-CSM-1/13, Center: Universitätsklinikum Salzburg [0104]
Patient No. 1: CRF Hardcopy, 18.09.2018 , 13:04:34

Screening/Start of run-in phase [14.03.2017]

Demographic information [CRF-page 1/15]	
Date of written informed consent (1/5)	**14**/**03**/20**17** [day/month/year]
Patient ID (2/5)	**01**-**04**-**001** (country-site-patient)
Patient year of birth (3/5)	19**51** [year] Age (at date of informed consent): **66** years
Gender (4/5)	**male**
Race of patient (5/5)	**white** if other - please specify: _____ _____ _____

Inclusion/exclusion criteria [CRF-page 2/15]	
Inclusion criteria	
Patient ⩾ 18 years (1/11)	**yes**
Male or female HD patients with a diagnosis of calciphylaxis (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching) (2/11)	**yes**
Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study (3/11)	**yes**
Exclusion criteria	
Sodium metabisulfite hypersensitivity, among others the history of bronchial asthma due to known sodium metabisulfite hypersensitivity (4/11)	**no**
Patients who have participated in any other investigational studies within 30 days previous to enrollment (5/11)	**no**
History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment (6/11)	**no**
Good response to conventional treatment (7/11)	**yes**
Life expectancy less than 4 months in the judgement of the investigator (8/11)	**no**
Comments (9/11)	_____ _____ _____

Clinical examination [CRF-page 3/15]	
Vital signs	
Date of assessment (1/24)	**15**/**03**/20**17** [day/month/year]
Body height (2/24)	**167** cm
Body weight (3/24)	**67.2** kg
Blood pressure (measured after patient has rested for 5 minutes) (4/24)	**154** mmHg / **94** mmHg [systolic/diastolic]
Heart rate (measured after patient has rested for 5 minutes) (5/24)	**67** b/min
BMI (calculated) (6/24)	**24.1** kg/m²
12-lead ECG	
ECG findings (7/24)	Date: **23**/**03**/20**17** [day/month/year] Result: **abnormal, not clinically relevant** if abnormal and clinically relevant - please specify: _____ _____ _____
Physical examination	

Were physical examinations performed (8/24)	**yes** if yes - date: **15**/**03**/20**17** [day/month/year]
Head (9/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Eye, ear, nose, throat (10/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Cardiovascular (11/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Dermatological (12/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Musculosceletal (13/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Respiratory (14/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Gastrointestinal (15/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Neurological (16/24)	**normal** if abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
	not done

Other (17/24)	if normal or abnormal - please specify: _____ _____ _____ if abnormal - clinically relevant: ___
Calciphylaxis diagnosis	
Calciphylaxis diagnosed according to typical signs and symptoms (18/24)	**yes** if yes - please check all that apply: [ ] Severe pain [ ] Livedo [ ] Violaceous plaques **[x] Ulcerations** [ ] Necroses if ulcerations and/or necroses - have other causes been excluded: **yes**
Tobacco use	
Tobacco use (19/24)	**Non-smoker**
Checklist	
Does the patient have any relevant medical history or concomitant diseases (20/24)	**yes**
Does the patient receive any concomitant medication (including pain medication) (21/24)	**yes**
Any concomitant procedures/measures performed (22/24)	**yes**
Has sample for biobanking been taken (23/24)	**no** if yes - date: __/__/20__ [day/month/year]
Comments (24/24)	_____ _____ _____

Hematology and venous blood gas analysis [CRF-page 4/15]	
Hematology	
Date of sample (1/12)	**15**/**03**/20**17** [day/month/year]
Patient's age at sampling date (2/12)	**[x] same as at informed consent** (**66** years) or ___ years
Hemoglobin (3/12)	**11 g/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
White blood cells (4/12)	**10.1 G/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (5/12)	_____ _____ _____
T50 Test (6/12)	___ min **[x] not available**
Venous blood gas analysis	
Partial pressure of oxygen (7/12)	**67 mmHg** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Partial pressure of oxygen venous (8/12)	_____.____ **mmHg** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Oxygen saturation (9/12)	**96 %** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____

Bicarbonate (10/12)	**26 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (11/12)	_____ _____ _____
Comments (12/12)	**"arterial" gas since dialysis Fistula!**

Clinical chemistry [CRF-page 5/15]	
Clinical Chemistry	
Date of sample (1/25)	**15**/**03**/20**17** [day/month/year]
Patient's age at sampling date (2/25)	**[x] same as at informed consent** (**66** years) or ___ years
IPTH (3/25)	**446 ng/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Calcium (4/25)	**2.57 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Phosphate (5/25)	**1.24 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Alk. phosphatase (6/25)	**76 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
pH serum (7/25)	**7.51 1/1** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
C-reactive protein (CRP) (8/25)	**0.8 mg/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Creatinine (9/25)	**6.9 mg/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Albumin (10/25)	**4.1 g/dl** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Sodium (11/25)	**137 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Potassium (12/25)	**6.4 mmol/l** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Chloride (13/25)	**98 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Magnesium (14/25)	**0.95 mmol/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
	14 U/l if outside normal limits - clinically relevant ? ___

GOT (AST) (15/25)	if clinically relevant - causal relationship with: _____
GPT (ALT) (16/25)	**18 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Gamma-GT (17/25)	**41 U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Amylase (18/25)	_____.____ **U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Lipase (19/25)	_____.____ **U/l** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
Urea (20/25)	**82 mg/dl** if outside normal limits - clinically relevant ? **no** if clinically relevant - causal relationship with: _____
Uric acid (21/25)	**4.4 mg/dl** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
1,25-Dihydroxy-Vitamine D (22/25)	_____.____ **pg/ml** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
25-Hydroxy-Vitamin D (23/25)	**46 ng/ml** if outside normal limits - clinically relevant ? ___ if clinically relevant - causal relationship with: _____
If "other" was chosen above for at least one time - please specify (24/25)	_____ _____ _____
Comments (25/25)	_____ _____ _____

Wound, pain and other assessments [CRF-page 6/15]	
Photo documentation and assessment of the wound area	
Was a photo documentation of all skin lesions performed (1/4)	**yes**
VAS for pain	
Was the degree of pain assessed by the patient on a visual analogue scale (2/4)	**yes** if yes - degree of pain: **4** mm
Comments (3/4)	_____ _____ _____

End of run-in phase

Inclusion/exclusion criteria [CRF-page 7/15]	
Inclusion criteria	
Patient $\geqslant$ 18 years (1/11)	**yes**
Male or female HD patients with a diagnosis of calciphylaxis. (Patients on peritoneal dialysis or patients with the requirement for renal replacement therapy, who are diagnosed with calciphylaxis, may be switched to HD and included in the study after switching). (2/11)	**yes**
Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study (3/11)	**yes**

Exclusion criteria	
Sodium metabisulfite hypersensitivity, among others the history of bronchial asthma due to known sodium metabisulfite hypersensitivity (4/11)	**no**
Patients who have participated in any other investigational studies within 30 days previous to enrollment (5/11)	**no**
History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment (6/11)	**no**
Good response to conventional treatment (7/11)	**yes**
Life expectancy less than 4 months in the judgement of the investigator (8/11)	**no**
Comments (9/11)	_____ _____ _____

Completion of run-in-phase [CRF-page 8/15]	
Has a skin biopsy been taken (1/7)	**no** if yes, date:__/__/20__ [day/month/year] if yes - calciphylaxis diagnosis confirmed by analysis: ___
Has the patient agreed to participate in the clinical trial and to undergo STS treatment (2/7)	**yes**
Disease status under BSC (3/7)	**initially stable disease**
Have all screening/baseline assessments been performed and is patient considered eligible for treatment start (4/7)	**no** if no - please check all that apply: [ ] patient did not meet all in-/exclusion criteria [ ] withdrawal of informed consent by the patient [ ] discretion of the investigator [ ] calciphylaxis diagnosis not confirmed **[x] other reason** if other reason - please specify: **improvement under conventional wound management**
Has all patient data been entered as far as possible and checked, all data can be set read-only (5/7)	**yes**
Comments (6/7)	_____ _____ _____

Lesions

Lesions [CRF-page 9/15] - Table	
Instance-no: 1 (Lesions)	
Lesion (1/25)	Lesion number: __ Lesion location: _____
Date of occurrence (2/25)	__/__/20__ [day/month/year] or [ ] before study start
Date of healing (3/25)	__/__/20__ [day/month/year] or [ ] still present
revised PWAT	
Photodocumentation VR (Run-in-phase) (4/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT VR (Dermatologist 1) (5/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type:

	_ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT VR (Dermatologist 2) (6/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V0 (7/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V0 (Dermatologist 1) (8/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V0 (Dermatologist 2) (9/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _

	Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V2 (10/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V2 (Dermatologist 1) (11/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V2 (Dermatologist 2) (12/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V3 (13/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V3 (Dermatologist 1) (14/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges:

	_ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V3 (Dermatologist 2) (15/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V4 (16/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V4 (Dermatologist 1) (17/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V4 (Dermatologist 2) (18/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _

	Total score: __
Photodocumentation V5 (19/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V5 (Dermatologist 1) (20/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Wound assessment and revPWAT V5 (Dermatologist 2) (21/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Photodocumentation V6 (22/25)	Date: __/__/20__ [day/month/year] or _____
Wound assessment and revPWAT V6 (Dermatologist 1) (23/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _

	Total score: __
Wound assessment and revPWAT V6 (Dermatologist 2) (24/25)	Initials Dermatologist: _ / _ [first/last name] Total wound area: ___.__ cm^2 or [ ] Wound area not assessed Size: _ Depth: _ Necrotic tissue type: _ Total amount of necrotic tissue: _ Granulation tissue type: _ Total amount of granulation tissue: _ Edges: _ Periulcer skin viability: _ Total score: __
Comments (25/25)	_____ _____ _____

Follow-up telephone interviews

Follow-up telephone interviews [CRF-page 10/15] - Table	
Instance-no: 1 (Follow-up telephone interviews)	
Follow-up telephone interview 1 Patient status [Instance-no: 1, page 1/1]	
Date of telephone call (1/7)	__/__/20__ [day/month/year]
Survival status	
Patient alive (2/7)	___
Disease status	
Is the disease still present (3/7)	___
Continuation STS-treatment	
Has the patient received further STS-treatment since last visit (4/7)	___
Further treatment	
Any further or additional treatment (5/7)	___
New calciphylaxis medication	
Any new medication for treatment of calciphylaxis (6/7)	___
Comments (7/7)	_____ _____ _____

End of study

End of study [CRF-page 11/15]	
Date of study end (1/6)	__/__/20__ [day/month/year]
Has the patient been listed on a transplant waiting list (2/6)	___ if yes, date: __/__/20__ [day/month/year]
Date of last contact when patient was alive (3/6)	__/__/20__ [day/month/year]
Reason of study end (4/6)	_____ if early discontinuation, lost to follow-up or other - please specify: _____ _____ _____ if patient died - date of death: __/__/20__ [day/month/year] [ ] not available reason of death: _____

	if other reason - please specify: _____ _____ _____
Has all patient data been entered as far as possible and checked, all data can be set read-only (5/6)	___
Comments (6/6)	_____ _____ _____

Medical history, concomitant medication and procedures, adverse events

Medical history [CRF-page 12/15] - Table	
Instance-no: 1 (Medical History)	
Condition (1/5)	_____
Start date (2/5)	__/__/____ [day/month/year] or [ ] unknown
End date (3/5)	__/__/____ [day/month/year] or _____
Treated with medications at study start (4/5)	___
Comments (5/5)	_____ _____ _____

Concomitant medication [CRF-page 13/15] - Table	
Instance-no: 1 (Concomitant Medication)	
Medication (Trade name) (1/8)	_____
Start date (2/8)	__/__/____ [day/month/year]
End date (3/8)	__/__/____ [day/month/year] or _____
Dose and frequency (4/8)	total daily dose and unit: _____ frequency: _____
Route of administration (5/8)	_____
Indication (6/8)	Medical history: (not available) or Adverse event: (not available) or Other: _____
Was the medication administered to treat pain (7/8)	___
Comments (8/8)	_____ _____ _____

Adverse event [CRF-page 14/15] - Table	
Instance-no: 1 (Adverse Event)	
Adverse event (1/9)	_____
Start date (2/9)	__/__/20__ [day/month/year]
Severity (3/9)	_____
Causal relationship to study treatment (4/9)	_____
Serious adverse event (5/9)	___ if yes - please check all that apply: [ ] death [ ] life-threatening [ ] inpatient hospitalization or prolongation of existing hospitalization [ ] persistent or significant disability/incapacity [ ] congenital anomaly/birth defect [ ] otherwise medically significant
Action taken with the IMP (6/9)	_____
	[ ] None [ ] Drug treatment [ ] Other if other - please specify:

Countermeasures (7/9)	_____ _____ _____
Outcome (8/9)	_____ if recovered/resolved or recovered/resolved with sequelae - please provide stop date: __/__/20__ [day/month/year]
Comments (9/9)	_____ _____ _____

Concomitant procedure/measure [CRF-page 15/15] - Table	
Instance-no: 1 (Concomitant Procedure/Measure)	
Procedure (1/5)	_____
Start date (2/5)	__/__/____ [day/month/year]
End date (3/5)	__/__/____ [day/month/year] or _____
Indication (4/5)	Medical history/concomitant disease: (not available) or Adverse event: (not available) or Other: _____
Comments (5/5)	_____ _____ _____

I confirm that I have carefully examined all entries of this patient. All information entered by myself or my colleagues is, to the best of my knowledge, correct as of the date below

Date: _____

Signature and stamp of investigator: _____