ASSIGN DMB

1. TITLE PAGE

Abbreviated 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

Name of Product/Test Drug/IMP:	Sodium Thiosulfate
Phase of Development:	2/3
Date of First Patient In:	14-Apr-2016
Date of Last Patient Out:	08-Feb-2018
Indication:	Treatment of calciphylaxis
Design:	The study design is a prospective, open, uncontrolled multicenter, Phase 2/3 clinical trial including various dialysis centers in Europe
Sponsor:	Dr. F. Köhler Chemie GmbH, Werner-von-Siemens-Str. 14-28, D-64625 Bensheim
Name of Sponsor Signatory:	Dr. Gernot Köhler
Date of Report (FINAL 1.0):	28-Mar-2019

This study was performed in accordance with Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and other applicable regulatory.

SIGNATURE PAGE

Protocol Title:	A Prospective Multicenter Phase 2/3 Clinical Trial with Sodium Thiosulfate for the Treatment of Calciphylaxis
Drug:	Sodium Thiosulfate
Indication:	Treatment of Calciphylaxis
Sponsor:	Dr. F. Köhler Chemie GmbH
Protocol Number:	STS-CSM-1/13

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

Sponsor

Dr. Gernot Köhler

_____ _____
Signature Date

Principal Investigator Site 0102

Dr. Karl Lhotta

_____ _____
Signature Date

Principal Investigator Site 0103

MD Andreas Vychytil

_____ _____
Signature Date

Principal Investigator Site 0104

Priv.-Doz. Dr. Hermann Salmhofer

_____ _____
Signature Date

Biostatistician (Assign Data Management and Biostatistics GmbH)

Dr. Anton Klingler

_____ _____
Signature Date

2. SYNOPSIS

<table>
<tr><td>Name of Company:
Dr. F. Köhler Chemie GmbH</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
N/A</td></tr>
<tr><td>Name of Active Ingredient:
Sodium Thiosulfate</td></tr>
<tr><td colspan="3">Title of Study:
A Prospective Multicenter Phase 2/3 Clinical Trial with Sodium Thiosulfate for the Treatment of Calciphylaxis</td></tr>
<tr><td colspan="3">Principal Investigators:
Dr. Karl Lhotta (Site 0102), MD Andreas Vychytil (Site 0103), Priv.-Doz. Dr. Hermann Salmhofer (Site 0104)</td></tr>
<tr><td colspan="3">Study Site(s):
Landeskrankenhaus Feldkirch, Abteilung für Nephrologie und Dialyse, Carinagasse 47, A-6800 Feldkirch
Medical University of Vienna, Department of Medicine III, Division of Nephrology and Dialysis, peritoneal dialysis unit, Währinger Gürtel 18-20, A-1090 Vienna
Universitätsklinikum Salzburg, Innere Medizin I, Dialyse-Station, Müllner Hauptstrasse 48, A-5020 Salzburg</td></tr>
<tr><td colspan="3">Publication (reference): None</td></tr>
<tr><td colspan="2">Study Dates:
First Patient Treated: 25-Jun-2016
Last Patient Completed: 08-Feb-2018
Study terminated by sponsor: 30-May-2018</td><td>Phase of Development: 2/3</td></tr>
</table>

Name of Company: Dr. F. Köhler Chemie GmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: N/A		
Name of Active Ingredient: Sodium Thiosulfate		

Objectives:

The objective of this project was 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 was established, during which patients were treated with conventional medications and measures. If the investigator observed typical symptoms of calciphylaxis (pain, appearance of more than one wound lesion) and decided that the patient was eligible for the treatment with STS and participation in the clinical trial, a biopsy was taken to confirm the diagnosis of calciphylaxis by excluding other causes of skin necroses and ulcerations. If a biopsy report of a consisting wound was available at Screening (VR) and the diagnosis of calciphylaxis was confirmed or other causes for necroses and ulcerations were excluded, an additional biopsy was not required.
- Patients with rapidly progressive disease under BSC were allocated to Group A while patients with less progressive or initially stable disease were allocated to Group B. Patients of both groups were treated with STS. Both patients groups were analysed separately, with the former to establish efficacy and the latter to be assessed descriptively. It was expected, that by far the majority of patients were in the progressor group.
- The run-in phase ended on the same day, when patients started treatment with STS (baseline, V0).
- Follow-up visits were performed after 4 (V1) 8 (V2), 16 (V3), 24 (V4), 36 (V5) and 48 weeks (V6) after start of STS treatment.

Name of Company: Dr. F. Köhler Chemie GmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: N/A		
Name of Active Ingredient: Sodium Thiosulfate		

Methodology:

The study design was a prospective, open, uncontrolled multicenter, Phase 2/3 clinical trial including various dialysis centers in Europe

Each patient served as his/her own control. A median reduction of at least 50% in total wound area at V4 compared to V0 was expected for patients treated with STS. This was far above the 20% wound reduction which was already considered as clinically relevant.

Patients with suspected calciphylaxis were 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 was up to 48 weeks after start of STS treatment.

Patients, who needed further treatment after the end of this clinical trial, were 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 were 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 Patients

Planned: 40

Screened: 5

Treated: 3

Diagnosis and Main Criteria for Inclusion:

Dialysis patients diagnosed with calciphylaxis, aged >= 18 years who provided informed consent.

Test Product, Dose and Mode of Administration, Batch Number:

Sodium Thiosulfate, 25 g per day given 3x per week as an infusion over 60 minutes starting 30 min before end of hemodialysis. Administered batch numbers: 1515211 (exp. May 2017), 1708711 (exp. 2019)

Duration of Treatment: 48 weeks after start of STS treatment
Reference Therapy, Dose, and Mode of Administration, Batch Number: Not applicable
Criteria for Evaluation: 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:

- 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.

Statistical Methods:

The main statistical analysis of the primary and secondary efficacy parameters was planned to be performed on subjects for whom infusion of study medication had been started, and for whom at least one post baseline measurement of the total wound area was available, using a pattern mixture model approach for missing data.
The primary efficacy variable percent reduction in the total wound area until V (24 weeks) was planned to be analyzed with a One-sample Wilcoxon signed rank test.
As the study was terminated early due to recruitment problems, no statistical analysis plan was written and no statistical analysis was performed.

Summary of Results:

Five subjects were screened and for three of those patients treatment was initiated. Two of the three treated patients were female, one was male. The treated patients were aged 55 to 82 years and all had rapidly progressive disease.

Patient 01-02-001 had received 25 mg study medication 3 times per week for 28 times. Patient 01-02-002 had received 25 mg study medication 3 times per week for 72 times and Patient 01-03-001 received 25 mg 3 times per week 30 times and 12.5 mg for 5 times due to Nausea and Cholestasis or Vomiting.

The following table shows an overview of adverse events reported in the study:

	Subjects with AE (N=3)	Number of AEs
Any AE	3	26
Any related AE	3	8
Any SAE	1	1
Any related SAE	0	0
Adverse events by severity		
Any mild AE	3	18
Any moderate AE	1	4
Any severe AE	2	4
Adverse events by severity		
Any mild AE	2	6
Any moderate AE	1	1
Any severe AE	1	1

In total 26 adverse events in all three subjects occurred. Eight of those 26 adverse events were considered as related to study medication (counting events assessed as related, probably related or possibly related). Only one serious adverse event occurred considered not related to study medication. Eighteen adverse events were graded mild, four were graded moderate and four were graded severe. Only one moderate adverse event was considered as probably related and one severe adverse event was considered as possibly related to study medication. Five mild graded adverse events were considered as probably related to study drug and only one mild graded adverse event as related.

Patient 01-02-001 and Patient 01-02-002 died 3-4 months after study entry. The reason of death for Patient 01-02-001 was not documented and the reason of death for Patient 01-02-002 was cerebral bleeding, respectively. Patient 01-03-001 was still alive at the end of the study.

All samples that had been collected during the course of the study were destroyed after the study was early terminated. No sample was analyzed.

Conclusions: No conclusions on the safety or efficacy of the treatment can be drawn due to the small sample size. However, for all three treated patients a decrease in pain and improvement of Clinical Global Impression was observed after STS treatment. No noticeable observations concerning safety were documented for the three treated subjects.
Date of Report: 28-Mar-2019

3. TABLE OF CONTENTS

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

5. ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents were 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 were a prerequisite for initiation of this clinical trial. The statement of EC contained the title of the trial, the trial code, the trial site, and a list of reviewed documents. It mentioned the date on which the decision was made and was officially signed by a committee member. This documentation also included a list of members of the EC present on the applicable EC meeting and a GCP compliance statement.

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

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

Persuant to GCP Ordinance, the EC and the regulatory authority were informed of all suspected serious unexpected adverse reactions (SUSARs), SAEs resulting in death and all AEs resulting in death or being life-threatening occurring during the trial. Both institutions were 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) was submitted once a year – Developmental Safety Update Report (DSUR).

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

5.2 ETHICAL CONDUCT OF THE STUDY

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

5.3 PATIENT INFORMATION AND CONSENT

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

A copy of the signed informed consent document was given to the patient. The documents were in a language understandable to the patient and specified who informed the patient.

The patients were informed as soon as possible if new information might influence his/her decision to participate in the trial. The communication of this information was documented.

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

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

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor's Representative	Dr. Gernot Köhler Dr. F. Köhler Chemie GmbH Werner-von-Siemens-Str. 14 - 28 64625 Bensheim Germany Phone: +49-6251-1083-0 Fax: +49-6251-1083-146
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Study Sites	
Site 0102	Landeskrankenhaus Feldkirch, Abteilung für Nephrologie und Dialyse, Carinagasse 47

Site 0103	Medical University of Vienna, Department of Medicine III, Division of Nephrology and Dialysis, peritoneal dialysis unit
Site 0104	Universitätsklinikum Salzburg, Innere Medizin I, Dialyse-Station
Clinical Laboratory	Site 0102: LKH Feldkirch Medizinisches Zentrallaboratorium Carinagasse 47, A-6800 Feldkirch Site 0103: Medical University Vienna Währinger Gürtel 18-20, A-1090 Wien Site 0104: Universitätsklinikum Salzburg Müllner Hauptstrasse 48, A-5020 Salzburg
Central laboratory	in.vent Diagnostica GmbH Dr. Diana Posselt Neuendorfstrasse 17 16761 Henningsdorf Germany Phone: +49 3302 55 119-33 CALCISCO AGE Seidenweg 12 P.O. Box (3010 Bern) 3012 Bern Suisse Phone: +41 78 763 93 66
Dermatologists	Universitätsklinikum Salzburg Prof. Dr. Martin Laimer Dr. Josef Koller Müllner Hauptstrasse 48 5020 Salzburg Austria
Statistics and Data Management	Assign Data Management and Biostatistics GmbH Stadlweg 23 6020 Innsbruck Austria Phone: +43 512 890 064 118 Fax: +43 512 281 514
Pharmacovigilance	Assign Safety Desk Assign Data Management and Biostatistics GmbH Stadlweg 23

6020 Innsbruck
Austria

7. INTRODUCTION

Calciphylaxis, also known as calcific uremic arteriolopathy (CUA), is a rare but catastrophic disease which mainly affects patients with end stage renal disease (ESRD). Unfortunately, to date there are neither approved therapies available for calciphylaxis, nor is there an established animal model to study its pathophysiology and to test potential treatment modalities.

Up to now, no prospective clinical trial with sodium thiosulfate (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.

8. STUDY OBJECTIVES

The objective of this project was to study the potentially beneficial effects of STS on the course and outcome of calciphylaxis. The study population should have consisted of 40 patients ≥ 18 years of age with calciphylaxis. Patients were treated with STS for at least 24 weeks. It was up to the discretion of the investigator to continue STS treatment.
The study design was 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 was expected to be up to 48 weeks plus the preceding 2 to 4 weeks run-in period.
The overall duration of the trial was expected to be approximately 4 years. The actual overall duration or recruitment varied.

8.1 PRIMARY AND SECONDARY ENDPOINTS

8.1.1 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.

8.1.2 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 was compared to baseline (V0) and assessed by a visual analogue scale (VAS) for pain (0-10). This was done directly before changing the wound dressing.
- Consumption of pain medication (normalized to morphine equivalent with an appropriate conversion table) was 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) was 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 was given when the patient was being actively listed on a transplant waiting list.

Bone mineral density (BMD):

For measurement of BMD, study sites were evaluated for the availability of Dual Energy X-ray absorptiometry (DEXA) technique.

- BMD was measured at V0 and after 48 weeks (V6)

Survival:

- Median overall survival after start of STS treatment
- One-year survival rate

8.1.3 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

8.1.4 Biobanking

- Serum was collected for assessing further relevant parameters, e.g. inflammatory and calcification parameters and bone turn-over markers. The evaluation of these parameters was 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).

9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

The study design was a prospective, open, uncontrolled multicenter, Phase 2/3 clinical trial including various dialysis centers in Europe

Each patient served as his/her own control. A median reduction of at least 50% in total wound area at V4 compared to V0 was expected for patients treated with STS. This was far above the 20% wound reduction which was already considered as clinically relevant.

Patients with suspected calciphylaxis were 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 was up to 48 weeks after start of STS treatment.

Patients, who needed further treatment after the end of this clinical trial, were 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 were 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.

9.2 SELECTION OF STUDY POPULATION

9.2.1 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

9.2.2 Exclusion Criteria

(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

9.2.3 Removal of Patients from Therapy or Assessment

Patients were free to withdraw from the study at any time for any reason. In addition, patients were 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 included reasons for patient withdrawals as well as details relevant to the patient withdrawal. If a patient withdrew from the trial prior to study completion, he/she underwent all procedures scheduled for study completion

9.3 TREATMENTS

9.3.1 Treatments Administered

The trial medication was administered only to patients included in this trial. Patients withdrawn from the trial retained their identification codes. New patients had always to have allocated a new identification code.

9.3.2 Identity of Investigational Product(s)

Property	Data
Code Name	STS
Chemical name	Sodium thiosulfate
Molecular Formula	$Na_2S_2O_3$
Molecular Weight	158,11 g/mol
Appearance	white crystals
Dose	25 g i.v. 3x per week

9.3.3 Method of assigning Patients to Treatment Groups

9.3.4 Selection of Doses in the Study

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

The dose of 25 g was 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 was reduced to 18.75 g or if appropriate, further lowered to 12.5 g. As soon as a better tolerability of STS had been achieved, the dose was 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 was 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 was only reduced for safety reasons.

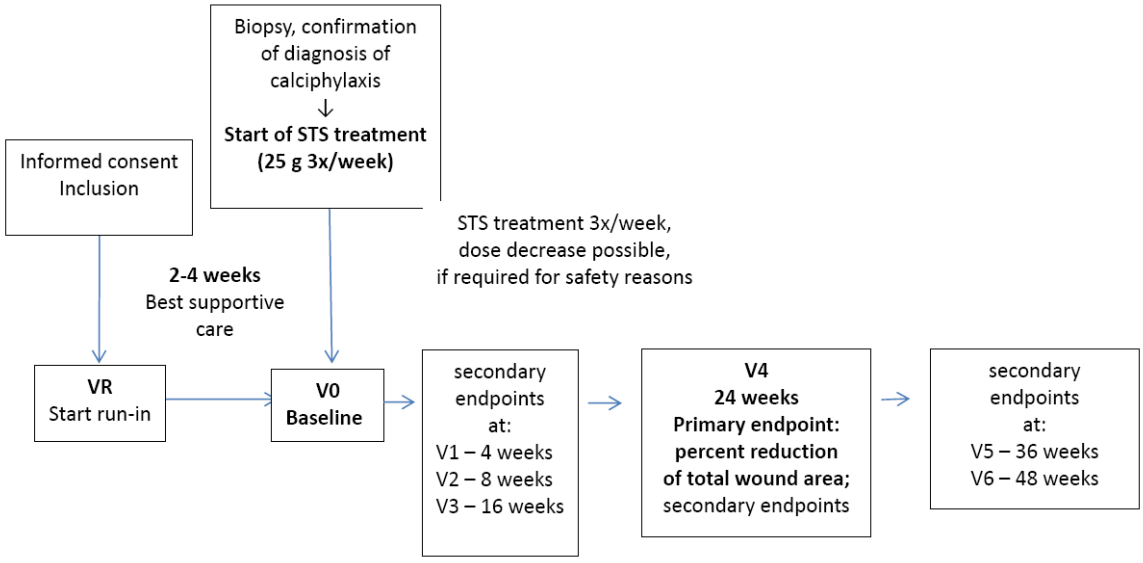
Time points of and reasons for any dose reduction or cessation of STS treatment was assessed in the eCRF.

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

Treatment was continued 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 occurred.

9.4 EFFICACY AND SAFETY VARIABLES

9.4.1 Flow Chart



9.4.2 Primary Efficacy Variable(s)

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

It was planned that the mean area of each wound of a given patient at a given time point should 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 took 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 could 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 dermatologists' assessments that were available at the time of study termination are described in 11.4.3. No statistical analysis of the primary and secondary endpoints was performed due to small sample size.

9.5 ASSESSMENTS WERE PERFORMED DATA QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the standard operating procedures of Assign Clinical Research GmbH and Assign Data Management and Biostatistics GmbH. Electronic CRFs were designed, implemented, validated and approved according to respective standard operating procedures. Accurate and reliable data collection was assured by verification and cross–check of the eCRFs against the Investigator's records by the Study Monitor (source document verification), and the maintenance of a drug–dispensing log by the Investigator. Data for this study were recorded via eCRF by the site from the source documents. Data were reviewed and checked for omissions, apparent errors, and values requiring further clarifications using computerized (automatic) and manual procedures. Data queries requiring clarification were communicated to the site for resolution via the eCRF. Only authorized personnel made corrections to the clinical database and an audit trail documented all corrections.

No audits or inspections were performed in this study.

9.6 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

There was 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 were known, secondly, a relatively high drop-out rate was expected based on data from the literature. Sample size was 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.

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.

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

9.7 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

The study had been terminated on 30-May-2018. Five subjects had been screened, three of them were found eligible for treatment start.

10. STUDY PATIENTS

10.1 DISPOSITION OF PATIENTS

In total five subjects were screened. Patient 01-04-001 (improvement under conventional wound management) and Patient 01-03-002 (patient did not meet all in-/exclusion criteria, calciphylaxis diagnosis not confirmed) were considered as screening failure.

The following subjects were found eligible for the study:

- Patient 01-02-001
- Patient 01-02-002
- Patient 01-03-001

All of these three subjects had received study medication at least once.

10.2 PROTOCOL DEVIATIONS

No protocol deviations had been collected.

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYZED

No analytical sets were analyzed. Results of the three subjects are described on the subject level in this report.

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The characteristics of the three subjects for whom treatment was started regarding year of birth, age at time of screening, sex and disease status are as follows:

- Patient 01-02-001, 1933, 82 years, male, rapidly progressive disease
- Patient 01-02-002, 1944, 72 years, female, rapidly progressive disease
- Patient 01-03-001, 1961, 55 years, female, rapidly progressive disease

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Subjects were treated on site. Treatment compliance was not assessed.

11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

11.4.1 Analysis of Efficacy

No analysis of efficacy parameters was performed. Results on the subject level are described in Section 11.4.3.

11.4.2 Statistical/Analytical Issues

Not applicable. No statistical analysis was performed.

11.4.2.1 Adjustments for Covariates

Not applicable. No statistical analysis was performed.

11.4.2.2 Handling of Dropouts or Missing Data

Not applicable. No statistical analysis was performed.

11.4.2.3 Interim Analyses and Data Monitoring

No interim analysis was planned or data monitoring was planned.

11.4.2.4 Multicenter Studies

Not applicable. No statistical analysis was performed.

11.4.2.5 Multiple Comparisons/Multiplicity

Not applicable. No statistical analysis was performed.

11.4.2.6 Use of a "Efficacy Subset" of Patients

Not applicable. No statistical analysis was performed.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

11.4.2.8 Examination of Subgroups

Not applicable. No statistical analysis was performed.

11.4.3 Tabulation of Individual Response Data

All lesions were starting before study start. Details on lesion assessments are shown in Table 1. Details on score components can be obtained from patient hardcopies (Section 16.3).

Table 1: Lesion Details (treated patients)

Patient	Lesion location	Time point	Date of Photo-documentation	Dermatologist 1		Dermatologist 2	
				Total wound area [cm²]	Total score	Total wound area [cm²]	Total score
01-02-001	Right calf pretibial (still present)	VR	14/04/2016	0	20	13,07	26
		V0	19/04/2016	0	28	35,57	25
		V2	14/06/2016	1,4	10	NA	5
	Right calf proximal (14/06/2016)	VR	14/04/2016	11,8	19	13,07	26
		V0	19/04/2016	0	27	28	25
		V2	14/06/2016	0	2	NA	0
	Left distal lateral calf (still present)	VR	14/04/2016	0,24	2	0,18	1
		V0	19/04/2016	0,29	3	0,3	20
		V2	14/06/2016	1	7	1,08	13
	Left distal medial calf (14/06/2016)	VR	14/04/2016	1,4	7	NA	0
		V0	19/04/2016	0,7	7	1,4	1
01-02-002	right lateral calf (30/11/2016)	VR	13/06/2016	2	21	2,514	18
		V0	16/06/2016	2,2	20	2,693	19
		V2	11/08/2016	0,15	3	NA	1
		V3	07/10/2016	0,11	3	0,229	1
		V4	30/11/2016	0,07	3	0,09	2
	Right claf ventral (still present)	VR	13/06/2016	0,16	3	0,18	2
		V0	16/06/2016	0,26	3	NA	1
	Right calf ventral below knee (11/08/2016)	VR	13/06/2016	0,17	3	0,05	2
		V0	16/06/2016	NA	3	NA	2
	Right first toe medial MCP-joint (30/11/2016)	VR	13/06/2016	0,5	8	0,07	0
		V0	16/06/2016	1,99	10	0,415	0
		V2	11/08/2016	0,43	11	1,865	9
		V3	07/10/2016	0,22	3	NA	1
		V4	30/11/2016	0,17	3	NA	0
01-003-001	Left limb, tibial (still present)	VR	07/04/2017	13,2	22	8,9	2
		V0	10/04/2017	27,1	21	NA	1
		V2	09/06/2017	1,9	24	NA	4
		V3	31/07/2017	89	26	0	2
	Left limb, calf (still present)	VR	07/04/2017	9,1	24	NA	1
		V0	10/04/2017	1,9	20	8,81	2
		V2	09/06/2017	8,1	19		6
		V3	31/07/2017			5,8	10
	Right limb, tibial (still present)	VR	07/04/2017	6	20	NA	1
		V0	10/04/2017	7,5	22	NA	1
		V2	09/06/2017	0,75	8	NA	0
		V3	31/07/2017	1,2	23	NA	0
	Right limb, calf (still present)	VR	07/04/2017	2,4	21	NA	1
		V0	10/04/2017	4,8	22	4,8	3
		V2	09/06/2017	60	14	NA	10
		V3	31/07/2017	63	NA	4	8

NA … Not assessed, VR … Run-in phase photo documentation, still present … still present at the time of the last assessment

Note that data cleaning activities after early termination of the study were limited and focused on subjects' safety. Lesion details and other efficacy parameters are to be interpreted cautiously. In particular, differences

between dermatologists' assessments may not be due to the subjectivity of the assessments, but lack of data cleaning and monitoring activities prior to database closure.

Visual analogue scale for pain measurements are shown in Table 2.

Table 2: Visual Analogue Scale for Pain (treated patients)

Patient	Time point	Visual Analogue Scale
01-02-001	Screening / Start of Run-in Phase	32
	Visit 0	58
	Visit 1	48
	Visit 2	21
01-02-002	Screening / Start of Run-in Phase	64
	Visit 0	21
	Visit 1	21
	Visit 2	43
	Visit 3	0
	Visit 4	0
	Visit 5	0
	Visit 6	0
01-03-001	Screening / Start of Run-in Phase	40
	Visit 0	7
	Visit 1	70
	Visit 2	48
	Visit 6	20

Thus, for all 3 patients, a decrease in pain was observed after STS treatment.

Reported CGI results are shown in Table 3.

Table 3: Clinical Global Impression (treated patients)

Patient	Time point	CGI Severity Scale	CGI Severity Scale
01-02-001	Visit 0	markedly ill	
	Visit 1	moderately ill	minimally improved
	Visit 2	moderately ill	much improved
01-02-002	Visit 0	mildly ill	
	Visit 1	normal, not at all ill	minimally improved
	Visit 2	mildly ill	minimally improved
	Visit 3	normal, not at all ill	very much improved since the initiation of treatment
	Visit 4	normal, not at all ill	minimally improved
	Visit 5	normal, not at all ill	very much improved since the initiation of treatment
	Visit 6	normal, not at all ill	much improved
01-03-001	Visit 0	moderately ill	
	Visit 1	markedly ill	much worse
	Visit 2	markedly ill	minimally worse
	Visit 6	markedly ill	minimally improved

CGI improvement was rated for Patient 01-02-001 at Visit 0 markedly ill, Visit 1 moderately ill (Improvement=minimally improved) and at Visit 2 moderately ill (Improvement=much improved). Patient 01-02-002 was rated at Visit 0 mildly ill, at Visit 1 normal not at all ill (Improvement=minimally improved), at Visit 2 mildly ill (Improvement=minimally improved), at Visit 3 mildly ill (Improvement=very much improved since the initiation of the treatment), at Visit 4 normal, not at all ill (Improvement=minimally improved), at Visit 5 normal, not at all ill (Improvement=very much improved since the initiation of the treatment) and at Visit 6 normal, not at all ill (Improvement=much improved). Patient 01-03-001 was rated at Visit 0 moderately ill, at Visit 1 markedly ill (Improvement=much worse), at Visit 2 markedly ill (Improvement=minimally worse) and at Visit 6 markedly ill (Improvement=minimally improved).

Bone mineral density was measured for Patient 01-02-001 at Visit 0 (t-Score: -4, z-Score: -2.5) and for Patient 01-02-002 at Visit 0 (t-Score: -3.9, z-Score: -1.9) and Visit 6 (t-Score: -3.7, z-Score: -1.7). The course of the BMD can be assessed only for one patient revealing no change after 11 months.

Death occurred in two patients: Patient 01-02-001 (Date of informed consent: 14-Mar-2016) on 26-Jul-2016 and Patient 01-02-002 (Date of informed consent: 10-Jun-2016) on 15-Sep-2017, see Section 12.3.1.1. Patient 01-03-001 (Date of informed consent: 07-Apr-2017) was still alive at the end of the study.

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

Not applicable.

11.4.5 Drug-Drug and Drug-Disease Interactions

Not applicable.

11.4.6 By-Patient Displays

No by-subject figures were produced. Details on assessments on the subjects-level are described in Section 11.4.3. Subject hardcopies are available in the attachment (Section 16).

11.4.7 Efficacy Conclusions

Due to the small sample size no efficacy conclusions can be drawn. However, for the three treated patients, a decrease in pain was observed after STS treatment and also CGI improved during STS treatment.

12. SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

Patient 01-02-001 had received 25 mg study medication 3 x per week for 28 times. Patient 01-02-002 had received 25 mg study medication 3 x per week for 72 times and Patient 01-03-001 received 25 mg 3 x per week 30 times and 12.5 mg for 5 times due to Nausea and Cholestasis or Vomiting.

12.2 ADVERSE EVENTS

In total 26 adverse events in all three subjects occurred. Eight of those 26 adverse events were considered as related to study medication. Only one serious adverse event occurred considered not related to study medication. Eighteen adverse events were graded mild, four were graded moderate and three were graded severe. Only one moderate adverse event was considered as probable related and one severe adverse event was considered as possibly related to study medication. Five mild graded adverse events were considered as probably related to study drug and only one mild graded adverse event as related.

Patient 01-02-001 experienced eight, Patient 01-02-002 experienced four and Patient 01-03-001 in total 14 adverse events.

The adverse events per Patient were the following:

Patient 01-02-001:

- Fracture of femoral neck which started on 22-Apr-2016 and ended on 03-May-2016 (severe, not related) and was considered as serious adverse event which required in-patient or prolonged hospitalization. No action was taken concerning the IMP, but surgery was performed.
- Otitis media right started on 10-May-2016 and ended on 20-May-2016 (mild, not related). Dose had not been changed but additional drug treatment was given.
- Nausea started on 28-Apr-2016 until 03-May-2016 (mild, probable related). Dose had not been changed but additional drug treatment was given.
- Emesis occurred 3 times- Two times from May-2016 until 14-May-2016 and until 20-May-2016 and additionally on 16-Jun-2016. All three events were graded mild and probable related to study drug. Dose had not been changed due to the adverse events but for the first and last event additional drug treatment had been given.
- Weight reduction from 14-Jun-2016 with unknown end date (mild, not related). Dose had not been changed and no action was taken.
- Hematoma periorbital left site from 14-Jun-2016 with unknown end date (mild, not related). Dose had not been changed and no action was taken.

Patient 01-02-002:

- Nausea during STS-administration on 21-Jun-2016 until 28-Nov-2016 (mild, related). Dose had not been changed but additional drug treatment had been given.
- Emesis on 18-Jun-2016 (mild, probable). No action had been taken also not regarding study drug.
- Cramps on 14-Jul-2016 (mild, not related). Dose had not been changed and no action had been taken.
- Relapse of Calciphylaxie started on 23-Jun-2017 with unknown end. Drug treatment had been given.

Patient 01-03-001

- Nausea started on 09-Apr-2017 which was not resolved (mild, unlikely). Dose had not been changed. Drug treatment had been given.
- Hypotension on 12-Apr-2017 until 13-Apr-2017 (mild, not related). Dose had not been changed, but Hemodialysis was not performed.
- Atrial fibrillation on 14-Apr-2017 (moderate, unlikely). Additional drug treatment had been given. No action was performed concerning study drug.
- Hypertensive crisis started on 15-Apr-2017 and ended on 16-Apr-2017 (mild, unlikely). Dose had not been changed. Drug treatment had been given.
- C. difficile – associated Diarrhea which started on 24-Apr-2017 until 05-May-2017 (mild, not related). Additional drug treatment had been given. No action was performed concerning study drug.
- C. difficile infection started on 22-May-2017 and ended on 19-Jul-2017 (mild, not related). No action had been taken.
- Calciphylaxis related necrosis started on 10-May-2017 which was not recovered (moderate, unlikely). Dose had not been changed, but debridement was performed.
- Vomiting started on 12-Apr-2017 which was not recovered (moderate, probable). Study drug had been withdrawn due to this adverse event. Furthermore, additional drug treatment was given.
- Cholestasis on 09-Jun-2017 (not recovered, moderate, unlikely). Dose had been reduced due to this Event. Other action taken was “Termination of drugs”.
- Drug induced liver injury on 10-Jul-2017 which was not recovered (severe, unlikely). Action taken regarding study drug was not applicable. All drugs which were not necessary were withdawn.
- Suspected drug induced liver injury started on 13-Jun-2017 and ended on 10-Jul-2017 (severe, unlikely). Dose had been reduced and other action taken was “Termination of other oral and i.v. drugs”.
- Undulating vomiting started on 11-Jul-2017 (not recovered, severe, possible related). Study drug was withdrawn due to this adverse event. Additional drug therapy had been given.

- Infection of unknown origin started on 28-Jun-2017 and ended on 09-Jul-2017 (mild, not related). Dose had not been changed but drug therapy had been given.
- Cytomegalovirus infection which started on 28-Apr-2017 until 02-May-2017. Study drug dosage had not been changed, additional drug therapy had been given.

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1 Deaths

No fatal adverse event was reported.

However, two patients' deaths were reported as end of study information. Patient 01-02-002 died due to Cerebral bleeding. Patient 01-02-001 also died due to unknown cause.

12.3.1.2 Other Serious Adverse Events

Only one serious adverse event occurred in Patient 01-02-001 (Fracture of femoral neck). The Event was considered as severe, but not related to study drug. It required in-patient or prolonged hospitalization. Surgery was performed due to this Event.

12.3.1.3 Significant Adverse Events

Not applicable.

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Primary Reporter Country: Austria, Subject: 02-001

Case: STS-01-02-001-01

Verbatim: **Fracture of femural neck**

Coded Term: **Femoral neck fracture (10016450)** [MedDRA v. 21.1]

A 83 year-old male Caucasian patient was enrolled in clinical trial STS-CSM-1/13, a prospective multicenter phase 2/3 clinical trial with Sodium Thiosulfate for the treatment of calciphylaxis.

On 22-Apr-2016 the patient was hospitalized due to pain in the right hip caused by a fall at home. A **fracture of the right femoral neck** was clinically and radiologically diagnosed. On 23-Apr-2016 a regular intermittent hemodialysis was done and afterwards the patient underwent a surgery.

The event became **serious** on 22-Apr-2016 and the patient was hospitalized on the same day.

The event was **recovered/resolved** on 03-May-2016.

The intensity of the event was assessed as **severe**.

The concomitant diseases CKD-MBD (Chronic kidney disease – mineral and bone disorder), dialysis-dependent chronic kidney disease and the patient's fall were provided as the causes of the event by the investigator.

The investigator assessed the causal relationship to the study drug STS as **not related,** the subject was not withdrawn from further study participation and no action was taken regarding the dose of the study drug.

The IMP STS i.v. 25 g was first administered on 19-Apr-2016 and the last administration prior to the SAE was done on 21-Apr-2016.

As countermeasure a surgery was documented.

Bisoprolol (Concor) oral 2.5 mg daily for atrial fibrillation since 16-Mar-2016, Tolterodin (Detrusitol) oral 1 mg daily for prostatic hyperplasia since 11-Mar-2016 and Buprenorphin (Transtec) transdermal 17.5 mcg for pain since 11-Mar-2016 were listed as **relevant concomitant medications taken at the time of the event**.

Laboratory on 22-Apr-2016 was provided as **relevant laboratory/diagnostic test**.

Results of laboratory on 22-Apr-2016:

Creatinine	3.0	mg/dl	0.7-1.2 (Normal range)
GFR-CKD/173m2	18	ml/min	>80
GGT	62	U/l	<60
Erythrocytes	3.44	T/l	4.60-5.70
Hemoglobin	99	g/l	144-175
Hematocrit	0.30	l/l	0.41-0.53

No **medications for treatment of SAE,** no **relevant adverse events,** no **relevant medical history** and no **other relevant risk factors** were documented.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Not applicable.

12.4 CLINICAL LABORATORY EVALUATION

Patient 0103/001 had in total 28 abnormal and clinically relevant laboratory values. Five of them at Screening / Start of Run-in Phase, six at Visit 0, ten at Visit 2 and seven at Visit 6. Most of them were considered due to underlying disease, five due to medical history and eight due to other reason (mostly adverse events).

Patient 0103/002 had in total seven clinically relevant abnormal laboratory values at Screening / Start of Run-in-Phase. 1,25-Dihydroxy-Vitamine D, 25-Hydroxy-Vitamin D, C-reactive protein, Creatinine, IPTH, Hemoglobin and White blood cells. Five of these values were due to medical history, two due to underlying disease.

Results on the subject level are contained in Appendix 16.

12.4.1 Evaluation of Each Laboratory Parameter

Results on the subject level are contained in Appendix 16.

12.5 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Results on the subject level are contained in Appendix 16.

12.6 SAFETY CONCLUSIONS

No conclusions on the safety of the treatment can be drawn due to the small sample size. No noticeable observations concerning safety were documented for the three treated subjects.

13. DISCUSSION AND OVERALL CONCLUSIONS

Only three patients were treated in the study before the trial was terminated early. No conclusions on the safety or efficacy of the STS treatment can be drawn due to the small sample size. For all three treated patients, a decrease in pain and improvement of Clinical Global Impression was observed after STS treatment. No noticeable observations concerning safety were documented.

In total 26 adverse events in all three treated subjects occurred. Eight of those 26 adverse events were considered as related to study medication. Only one serious adverse event occurred considered not related to study medication. Eighteen adverse events were graded mild, four were graded moderate and three were graded severe. Only one moderate adverse event was considered as probable related and one severe adverse event was considered as possibly related to study medication. Five mild graded adverse events were considered as probably related to study drug and only one mild graded adverse event as related.

Two patients died 3-4 months after study entry. One patient was still alive at the end of the study.

All samples that had been collected during the course of the study were destroyed after the study was early terminated. No sample was analyzed.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Not applicable. No statistical analysis was performed.

15. REFERENCE LIST

Not applicable.

16. APPENDICES

Appendices are provided in a separate document.