

**Clinical trial results:****A Prospective Multicenter Phase 2/3 Clinical Trial with Sodium Thiosulfate for the Treatment of Calciphylaxis****Summary**

EudraCT number	2014-002128-28
Trial protocol	DE AT
Global end of trial date	30 May 2018

Results information

Result version number	v1 (current)
This version publication date	04 July 2019
First version publication date	04 July 2019
Summary attachment (see zip file)	Clinical Study Report version 1.0 with Synopsis (01a_STS_CSM_1_13_Clinical_Study_Report_FINAL_1_0.pdf) Appendix to Clinical Study Report (02_STS_CSM_1_13_CSR_Appendix_16_FINAL_1_0.pdf) CSR signature page Sponsor and Data Management (01b_20190404_STS-CSM-1_13_CSR_SignPage_Klingler_Köhler.pdf) CSR Signature Page Principal Investigator Site Feldkirch Austria (01c_20190401_STS-CSM-1_13_CSR_SignPage_Lhotta.pdf) CSR Signature Page Coordinating Investigator Site Salzburg Austria (01d_20190401_STS-CSM-1_13_CSR_SignPage_Salmhofer.pdf) CSR Signature Page Principal Investigator Site Vienna Austria (01e_20190416_STS-CSM-1_13_CSR_SignPage_Vychytil.pdf)

Trial information**Trial identification**

Sponsor protocol code	STS-CSM-1/13
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Additional study identifiers

ISRCTN number	ISRCTN73380053
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Franz Köhler Chemie GmbH
Sponsor organisation address	Werner-von-Siemens-Str. 14-28, Bensheim, Germany, 64625
Public contact	Leitung Klinische Forschung, Dr. Franz Köhler Chemie GmbH, 0049 625110830,
Scientific contact	Leitung Klinische Forschung, Dr. Franz Köhler Chemie GmbH, 0049 625110830,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 May 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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.

Protection of trial subjects:

During the run-in phase, measures for best supportive care that were considered obligatory were cautious necrosectomy (without debridement of wound margins) and support wound healing by keeping patients dry and treating peripheral edema. In addition, all participating study sites were free in their decision how to treat their calciphylaxis patients during the run-in phase.

Patients who needed further treatment after the end of this clinical trial were treated according to the current best standard of care at the respective study site.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	14 April 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 5
Worldwide total number of subjects	5
EEA total number of subjects	5

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	2
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Territories: Austria, Germany, Switzerland

Planned recruitment start date: 15-Jul-2015

Effective recruitment start date: 28-Jan-2016

First subject recruited on: 14-Apr-2016

Last subject recruited on: 17-Jan-2018

Clinical Trial stopped prematurely on: 30-May-2018

Pre-assignment

Screening details:

Dialysis patients with suspected calciphylaxis were asked to participate. During a run-in phase of 2-4 weeks with conventional wound management (c.w.m.) diagnosis of calciphylaxis was confirmed and efficacy of c.w.m. assessed. Patients with unconfirmed calciphylaxis or good response to c.w.m. after run-in phase were considered screening failures.

Pre-assignment period milestones

Number of subjects started	5
Number of subjects completed	3

Pre-assignment subject non-completion reasons

Reason: Number of subjects	good response to conventional wound management: 1
Reason: Number of subjects	calciphylaxis diagnosis not confirmed: 1

Period 1

Period 1 title	V0
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Group A
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Arm description:

Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.

Arm type	Experimental
Investigational medicinal product name	Sodium Thiosulfate (STS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 25 g

Frequency: 3 times per week during haemodialysis

Infusion start: 30 minutes before end of haemodialysis

Infusion duration: 60 minutes

Number of subjects in period 1 ^[1]	Group A
Started	3
Treatment Start	3
Completed	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Five subjects were screened and entered the run-in phase. Two of the five subjects proved to be ineligible and did not enter the baseline period. Therefore, only three subjects are reported in the baseline period.

Period 2

Period 2 title	V1
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Group A
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Arm description:

Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.

Arm type	Experimental
Investigational medicinal product name	Sodium Thiosulfate (STS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 25 g

Frequency: 3 times per week during haemodialysis

Infusion start: 30 minutes before end of haemodialysis

Infusion duration: 60 minutes

Number of subjects in period 2	Group A
Started	3
Completed	3

Period 3

Period 3 title	V2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Group A
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Arm description:

Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.

Arm type	Experimental
Investigational medicinal product name	Sodium Thiosulfate (STS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 25 g

Frequency: 3 times per week during haemodialysis

Infusion start: 30 minutes before end of haemodialysis

Infusion duration: 60 minutes

Number of subjects in period 3	Group A
Started	3
Completed	3

Period 4

Period 4 title	V3
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Group A
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Arm description:

Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.

Arm type	Experimental
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Investigational medicinal product name	Sodium Thiosulfate (STS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 25 g

Frequency: 3 times per week during haemodialysis

Infusion start: 30 minutes before end of haemodialysis

Infusion duration: 60 minutes

Number of subjects in period 4	Group A
Started	3
Completed	1
Not completed	2
Adverse event, non-fatal	1
subject decided to discontinue hemodialysis	1

Period 5

Period 5 title	V4
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Group A
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Arm description:

Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.

Arm type	Experimental
Investigational medicinal product name	Sodium Thiosulfate (STS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 25 g

Frequency: 3 times per week during haemodialysis

Infusion start: 30 minutes before end of haemodialysis

Infusion duration: 60 minutes

Number of subjects in period 5	Group A
Started	1
Primary Endpoint Assessment	1
Completed	1

Period 6

Period 6 title	V5
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Group A
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Arm description:

Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.

Arm type	Experimental
Investigational medicinal product name	Sodium Thiosulfate (STS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 25 g

Frequency: 3 times per week during haemodialysis

Infusion start: 30 minutes before end of haemodialysis

Infusion duration: 60 minutes

Investigational medicinal product name	Sodium Thiosulfate (STS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 25 g

Frequency: 3 times per week during haemodialysis

Infusion start: 30 minutes before end of haemodialysis

Infusion duration: 60 minutes

Number of subjects in period 6	Group A
Started	1
Completed	1

Period 7

Period 7 title	V6 / End of Treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Group A
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Arm description:

Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.

Arm type	Experimental
Investigational medicinal product name	Sodium Thiosulfate (STS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 25 g

Frequency: 3 times per week during haemodialysis

Infusion start: 30 minutes before end of haemodialysis

Infusion duration: 60 minutes

Number of subjects in period 7	Group A
Started	1
End of Study	2
Completed	2

Joined	1
Early Termination Visit	1

Period 8

Period 8 title	Survival Follow Up 1
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Group A
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Arm description:

Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.

Arm type	Experimental
Investigational medicinal product name	Sodium Thiosulfate (STS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 25 g

Frequency: 3 times per week during haemodialysis

Infusion start: 30 minutes before end of haemodialysis

Infusion duration: 60 minutes

Number of subjects in period 8	Group A
Started	2
Completed	1
Not completed	1
Lost to follow-up	1

Period 9

Period 9 title	Survival Follow Up 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Group A
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Arm description:

Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.

Arm type	Experimental
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Investigational medicinal product name	Sodium Thiosulfate (STS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 25 g

Frequency: 3 times per week during haemodialysis

Infusion start: 30 minutes before end of haemodialysis

Infusion duration: 60 minutes

Number of subjects in period 9	Group A
Started	1
Completed	0
Not completed	1
Subject's death	1

Baseline characteristics

Reporting groups

Reporting group title	Group A
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Reporting group description:

Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.

Reporting group values	Group A	Total	
Number of subjects	3	3	
Age categorical			
Units: Subjects			
Adults (18-64 years)	1	1	
From 65-84 years	2	2	
Gender categorical			
Units: Subjects			
Female	2	2	
Male	1	1	
Ethnicity			
Units: Subjects			
white	3	3	
black	0	0	
asiatic	0	0	
other	0	0	

End points

End points reporting groups

Reporting group title	Group A
Reporting group description: Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.	
Reporting group title	Group A
Reporting group description: Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.	
Reporting group title	Group A
Reporting group description: Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.	
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Reporting group title	Group A
Reporting group description: Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.	
Reporting group title	Group A
Reporting group description: Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.	

Primary: Percent reduction of the total wound area after 24 weeks (v4) compared to baseline (V0).

End point title	Percent reduction of the total wound area after 24 weeks (v4) compared to baseline (V0). ^[1]
End point description: 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. Note: No statistical analysis of the primary endpoint was performed due to small sample size.	
End point type	Primary
End point timeframe: Baseline (V0), 24 weeks (V4)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the study was terminated early due to recruitment problems, no statistical analysis plan was written and no statistical analysis was performed.

End point values	Group A	Group A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[2]	0 ^[3]		
Units: square centimeter				
arithmetic mean (standard deviation)	()	()		

Notes:

[2] - No statistical analysis of the primary endpoint was performed due to small sample size.

[3] - No statistical analysis of the primary endpoint was performed due to small sample size.

Statistical analyses

No statistical analyses for this end point

Secondary: Total wound area at 8, 16, 36, 48 weeks compared to baseline (V0).

End point title	Total wound area at 8, 16, 36, 48 weeks compared to baseline (V0).
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End point description:

Status of skin lesions

Note: No statistical analysis of the secondary endpoints was performed due to small sample size. Lesion details can be found in attachment (table 1: Lesion Details (treated patients)).

End point type	Secondary
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End point timeframe:

Baseline, 8 weeks, 16 weeks, 36 weeks and 48 weeks after start of treatment

End point values	Group A	Group A	Group A	Group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[4]	0 ^[5]	0 ^[6]	0 ^[7]
Units: square centimeter				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[4] - No statistical analysis was performed due to small sample size.

[5] - No statistical analysis was performed due to small sample size.

[6] - No statistical analysis was performed due to small sample size.

[7] - No statistical analysis was performed due to small sample size.

End point values	Group A			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[8]			
Units: square centimeter				
arithmetic mean (standard deviation)	()			

Notes:

[8] - No statistical analysis was performed due to small sample size.

Attachments (see zip file)	Table 1: Lesion Details (treated patients)/Table 1.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Complete remission of wound area at any point

End point title	Complete remission of wound area at any point
End point description:	
Status of skin lesions.	
Note: No statistical analysis of the secondary endpoints was performed due to small sample size. Occurrence was assessed using the results of the photo documentation of the lesions. Lesion details can be found in attachment of endpoint "Total wound area at 8, 16, 36, 48 weeks compared to baseline (V0)" (table 1: Lesion Details (treated patients)).	
End point type	Secondary
End point timeframe:	
V0 (Baseline) to V6 (48 weeks / End of Treatment)	

End point values	Group A	Group A	Group A	Group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	0 ^[9]	3	1 ^[10]
Units: Occurrence				
Complete remission of wound area	0		0	0

Notes:

[9] - No photodocumentation was scheduled for V1 (4 weeks). No further documentation available.

[10] - Only one subject completed this arm.

End point values	Group A	Group A	Group A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	1	1 ^[11]	
Units: Occurrence				
Complete remission of wound area	0	1	0	

Notes:

[11] - Early Termination Visit Subject 0103-001 (V3 in table 1)

No photodocumentation of subject 0102-002.

Statistical analyses

No statistical analyses for this end point

Secondary: Qualitative Improvement of skin lesions at 8, 16, 24, 36, 48 weeks

End point title	Qualitative Improvement of skin lesions at 8, 16, 24, 36, 48 weeks
End point description:	
Status of skin lesions.	
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.	
Note: No statistical analysis of the secondary endpoints was performed due to small sample size. Lesion details can be found in attachment of endpoint "Total wound area at 8, 16, 36, 48 weeks compared to baseline (V0)" (table 1: Lesion Details (treated patients)).	
End point type	Secondary

End point timeframe:

V0 (Baseline), V2 (8 weeks), V3 (16 weeks), V4 (24 weeks), V5 (36 weeks), V6 (48 weeks, End of Treatment).

End point values	Group A	Group A	Group A	Group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[12]	0 ^[13]	0 ^[14]	0 ^[15]
Units: revPWAT score				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[12] - No statistical analysis was performed due to small sample size.

[13] - No statistical analysis was performed due to small sample size.

[14] - No statistical analysis was performed due to small sample size.

[15] - No statistical analysis was performed due to small sample size.

End point values	Group A	Group A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[16]	0 ^[17]		
Units: revPWAT score				
arithmetic mean (standard deviation)	()	()		

Notes:

[16] - No statistical analysis was performed due to small sample size.

[17] - No statistical analysis was performed due to small sample size.

Statistical analyses

No statistical analyses for this end point

Secondary: Use of wound debridement

End point title	Use of wound debridement
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End point description:

Status of skin lesions.

Note: No statistical analysis of the secondary endpoints was performed due to small sample size. Data shown represent the documented corresponding concomitant procedures that were reported at the respective visit, if applicable. Results on subject level are contained in the CSR Appendix 16 that is attached in the Index section.

End point type	Secondary
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End point timeframe:

V0 (Start of Treatment) to V6 (week 48 / End of Study including Early Termination)

End point values	Group A	Group A	Group A	Group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	1 ^[18]
Units: time(s)				
Wound debridement was performed	0	1	1	0

Notes:

[18] - Only one subject completed this arm.

End point values	Group A	Group A	Group A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	1	2 ^[19]	
Units: time(s)				
Wound debridement was performed	0	0	0	

Notes:

[19] - Early Termination Visit of subject 01-03-001.

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction of pain in the areas of calciphylaxis after 4, 8, 16, 24, 36 and 48 weeks after start of STS treatment

End point title	Reduction of pain in the areas of calciphylaxis after 4, 8, 16, 24, 36 and 48 weeks after start of STS treatment
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End point description:

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.

Note: No statistical analysis was performed on secondary endpoints due to small sample size. A summary of the results is attached (table 2: Visual Analogue Scale for Pain (treated patients)).

End point type	Secondary
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End point timeframe:

V0 (Baseline), V1 (4 weeks), V2 (8 weeks), V3 (16 weeks), V4 (24 weeks), V5 (36 weeks), V6 (48 weeks)

End point values	Group A	Group A	Group A	Group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[20]	0 ^[21]	0 ^[22]	0 ^[23]
Units: millimeter(s)				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[20] - No statistical analysis was performed due to small sample size.

[21] - No statistical analysis was performed due to small sample size.

[22] - No statistical analysis was performed due to small sample size.

[23] - No statistical analysis was performed due to small sample size.

End point values	Group A	Group A	Group A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[24]	0 ^[25]	0 ^[26]	
Units: millimeter(s)				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[24] - No statistical analysis was performed due to small sample size.

[25] - No statistical analysis was performed due to small sample size.

[26] - No statistical analysis was performed due to small sample size.

Attachments (see zip file)	Table 2: VAS for Pain (treated patients)/Table 2.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of pain medication

End point title	Consumption of pain medication
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End point description:

Pain evaluation.

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).

Note: No statistical analysis was performed on secondary endpoints due to small sample size. Results on subject level are contained in the CSR Appendix 16 that is attached in the Index section.

End point type	Secondary
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End point timeframe:

VR (screening), V0 (baseline), V1 (4 weeks), V2 (8 weeks), V3 (16 weeks), V4 (24 weeks), V5 (36 weeks), V6 (48 weeks, End of Study)

End point values	Group A	Group A	Group A	Group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[27]	0 ^[28]	0 ^[29]	0 ^[30]
Units: milligram(s)				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[27] - No statistical analysis was performed due to small sample size.

[28] - No statistical analysis was performed due to small sample size.

[29] - No statistical analysis was performed due to small sample size.

[30] - No statistical analysis was performed due to small sample size.

End point values	Group A	Group A	Group A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[31]	0 ^[32]	0 ^[33]	
Units: milligram(s)				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[31] - No statistical analysis was performed due to small sample size.

[32] - No statistical analysis was performed due to small sample size.

[33] - No statistical analysis was performed due to small sample size.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical global impression as assessed by the Clinical Global Impressions-Severity scale.

End point title	Clinical global impression as assessed by the Clinical Global Impressions-Severity scale.
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End point description:

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).

No statistical analysis was performed due to small sample size. A summary of the results is attached (table 3: Clinical Global Impression (treated patients)).

End point type	Secondary
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End point timeframe:

V0 (baseline), V1 (4 weeks), V2 (8 weeks), V3 (16 weeks), V4 (24 weeks), V5 (36 weeks), V6 (48 weeks / End of Study)

End point values	Group A	Group A	Group A	Group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[34]	0 ^[35]	0 ^[36]	0 ^[37]
Units: CGI-S scale				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[34] - No statistical analysis was performed due to small sample size.

[35] - No statistical analysis was performed due to small sample size.

[36] - No statistical analysis was performed due to small sample size.

[37] - No statistical analysis was performed due to small sample size.

End point values	Group A	Group A	Group A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[38]	0 ^[39]	0 ^[40]	
Units: CGI-S scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[38] - No statistical analysis was performed due to small sample size.

[39] - No statistical analysis was performed due to small sample size.

[40] - No statistical analysis was performed due to small sample size.

Attachments (see zip file)	Table 3: CGI (treated patients)/Table 3.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: 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 CGI-S.

End point title	Change in clinical global impression as assessed by the Clinical
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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 CGI-S.

End point description:

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). A summary of the results is attached at endpoint "Clinical global impression as assessed by the Clinical Global Impressions-Severity scale" (table 3: Clinical Global Impression (treated patients)).

End point type	Secondary
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End point timeframe:

V1 (4 weeks), V2 (8 weeks), V3 (16 weeks), V4 (24 weeks), V5 (36 weeks), V6 (48 weeks / End of Study)

End point values	Group A	Group A	Group A	Group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[41]	0 ^[42]	0 ^[43]	0 ^[44]
Units: CGI-I score				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[41] - No statistical analysis was performed due to small sample size.

[42] - No statistical analysis was performed due to small sample size.

[43] - No statistical analysis was performed due to small sample size.

[44] - No statistical analysis was performed due to small sample size.

End point values	Group A	Group A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[45]	0 ^[46]		
Units: CGI-I score				
arithmetic mean (standard deviation)	()	()		

Notes:

[45] - No statistical analysis was performed due to small sample size.

[46] - No statistical analysis was performed due to small sample size.

Statistical analyses

No statistical analyses for this end point

Secondary: Improvement leading to eligibility of the patient for kidney transplantation.

End point title	Improvement leading to eligibility of the patient for kidney transplantation.
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End point description:

Eligibility for kidney transplantation was given when the patient was being actively listed on a transplant waiting list. This did not occur for any patient in this clinical trial.

End point type	Secondary
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End point timeframe:

V0 (Baseline) to V6 (48 weeks / End of Study)

End point values	Group A	Group A	Group A	Group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	1 ^[47]
Units: Occurrence				
Actively listed on a transplant waiting list	0	0	0	0

Notes:

[47] - Only one subject completed this arm.

End point values	Group A	Group A	Group A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	1	2 ^[48]	
Units: Occurrence				
Actively listed on a transplant waiting list	0	0	0	

Notes:

[48] - Early Termination Visit of Subject 01-03-001.

Statistical analyses

No statistical analyses for this end point

Secondary: Bone mineral density

End point title	Bone mineral density
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End point description:

Measurement of bone mineral density was optional.

Note: No statistical analysis was performed due to small sample size. Results on subject level are contained in the CSR Appendix 16 that is attached in the Index section.

End point type	Secondary
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End point timeframe:

V0 (Baseline), V6 (48 weeks / End of Study)

End point values	Group A	Group A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[49]	0 ^[50]		
Units: t/z-score				
arithmetic mean (standard deviation)	()	()		

Notes:

[49] - No statistical analysis was performed due to small sample size.

[50] - No statistical analysis was performed due to small sample size.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival after start of STS treatment

End point title	Overall survival after start of STS treatment
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End point description:

Median overall survival after start of STS treatment

Note: No statistical analysis for secondary endpoints was performed due to small sample size. Results on subject level are contained in the CSR Appendix 16 that is attached in the Index section.

End point type	Secondary
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End point timeframe:

V0 (Baseline/Start of Treatment) - Survival Follow up 2

End point values	Group A			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[51]			
Units: percent				
number (not applicable)				

Notes:

[51] - No analysis was performed due to small sample size.

Statistical analyses

No statistical analyses for this end point

Secondary: One-year survival rate

End point title	One-year survival rate
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End point description:

Note: No statistical analysis for secondary endpoints was performed due to small sample size. Results on subject level are contained in the CSR Appendix 16 that is attached in the Index section.

End point type	Secondary
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End point timeframe:

VR (run-in phase) to SFU 2 (survival follow-up 12 months after End of Study)

End point values	Group A			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[52]			
Units: percent				
number (not applicable)				

Notes:

[52] - No analysis was performed due to small sample size.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Safety Parameters

End point title	Safety Parameters
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End point description:

The following safety parameters were monitored: Adverse events including Serious Adverse Events and Adverse Events of Special Interest, 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) and tolerability of STS treatment (dose reduction due to adverse event).

Note: No statistical analysis was performed due to small sample size. Results on subject level are contained in the CSR Appendix 16 that is attached in the Index section.

End point type	Other pre-specified
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End point timeframe:

V0 (start of treatment) to V6 (End of Study)

End point values	Group A	Group A	Group A	Group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[53]	0 ^[54]	0 ^[55]	0 ^[56]
Units: unit(s)				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[53] - No statistical analysis was performed due to small sample size.

[54] - No statistical analysis was performed due to small sample size.

[55] - No statistical analysis was performed due to small sample size.

[56] - No statistical analysis was performed due to small sample size.

End point values	Group A	Group A	Group A	Group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[57]	0 ^[58]	0 ^[59]	0 ^[60]
Units: unit(s)				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[57] - No statistical analysis was performed due to small sample size.

[58] - No statistical analysis was performed due to small sample size.

[59] - No statistical analysis was performed due to small sample size.

[60] - No statistical analysis was performed due to small sample size.

End point values	Group A			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[61]			
Units: unit(s)				
arithmetic mean (standard deviation)	()			

Notes:

[61] - No statistical analysis was performed due to small sample size.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Biobanking

End point title	Biobanking
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End point description:

In order to establish a biobank for calciphylaxis, 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. Due to the small sample size this plan was not realized after the early termination of the study. The samples were discarded.

End point type	Other pre-specified
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End point timeframe:

VR (run-in phase), V0 (baseline), V2 (8 weeks), V3 (16 weeks), V4 (24 weeks), V6 (48 weeks, End of Study)

End point values	Group A	Group A	Group A	Group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[62]	0 ^[63]	0 ^[64]	0 ^[65]
Units: Serum sample(s)				

Notes:

[62] - No serum sample analysis was performed due to small sample size.

[63] - No serum samples were analyzed due to small sample size.

[64] - No serum samples were analyzed due to small sample size.

[65] - No serum samples were analyzed due to small sample size.

End point values	Group A			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[66]			
Units: Serum sample(s)				

Notes:

[66] - No serum samples were analyzed due to low sample size.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: T50 test

End point title	T50 test
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End point description:

The T50 test was planned to be conducted to obtain information on the calcification propensity by monitoring the maturation time (T50) of calciprotein particles in serum. The evaluation of these parameters was planned to be performed within 5 years after the end of the trial. Due to the small sample size this plan was not realized after the early termination of the study. The samples were discarded.

End point type	Other pre-specified
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End point timeframe:

VR (run-in phase), V0 (baseline), V2 (8 weeks), V3 (16 weeks), V4 (24 weeks), V6 (48 weeks, End of Study)

End point values	Group A	Group A	Group A	Group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[67]	0 ^[68]	0 ^[69]	0 ^[70]
Units: minute(s)				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[67] - No serum samples were analyzed due to small sample size.

[68] - No serum samples were analyzed due to small sample size.

[69] - No serum samples were analyzed due to small sample size.

[70] - No serum samples were analyzed due to small sample size.

End point values	Group A			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[71]			
Units: minute(s)				
arithmetic mean (standard deviation)	()			

Notes:

[71] - No serum samples were analyzed due to small sample size.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From V0 (Baseline / Start of Treatment) to V6 (End of Study / End of Treatment)

Adverse event reporting additional description:

Adverse events of special interest were defined as incidences of infections and sepsis, metabolic acidosis, ventricular tachycardia, hypotension and bone fractures.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Group A
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Reporting group description:

Patients with rapidly progressive disease under conventional wound management. Analysis to establish efficacy.

Serious adverse events	Group A		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Musculoskeletal and connective tissue disorders			
Fracture of femoral neck	Additional description: required inpatient hospitalization or prolongation of existing hospitalization		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Group A		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Cardiac disorders			
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Atrial fibrillation			

subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Hypertensive crisis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Cramps			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Otitis media right			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	3 / 3 (100.00%)		
occurrences (all)	5		
Nausea during IMP administration	Additional description: during STS administration		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Diarrhoea	Additional description: Clostridium difficile associated		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Undulating vomiting			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Drug-induced liver injury			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		

Skin and subcutaneous tissue disorders			
	Additional description: periorbital left side		
	Haematoma		
	subjects affected / exposed	1 / 3 (33.33%)	
	occurrences (all)	1	
	Additional description: related to calciphylaxis		
	Necrosis		
	subjects affected / exposed	1 / 3 (33.33%)	
Infections and infestations	occurrences (all)	1	
	Clostridium difficile infection		
	subjects affected / exposed	1 / 3 (33.33%)	
	occurrences (all)	1	
	Additional description: of unknown origin		
	Cytomegalovirus infection		
	subjects affected / exposed	1 / 3 (33.33%)	
	occurrences (all)	1	
Metabolism and nutrition disorders	Weight decreased		
	subjects affected / exposed	1 / 3 (33.33%)	
	occurrences (all)	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 February 2017	<p>In the submission process in Switzerland the Swissethics requested adaptations in the Clinical Study Protocol (CSP) that was previously approved in Austria and Germany. The substantial amendment aimed to harmonize the CSP in all participating countries.</p> <p>The substantial changes were:</p> <ul style="list-style-type: none">- change of responsible statistician- sponsor address- CRO name change- contact details for SAE reporting- additional information that 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- establishing that all female subjects with childbearing potential have to perform a pregnancy test at every study visit- addition of definitions for the term post-menopausal and for effective methods of birth control in the exclusion criteria section- generalization of countries involved in the study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

- | |
|---|
| <ul style="list-style-type: none">- early termination due to low recruitment- only 5 of 40 planned subjects were enrolled in 3 years. 3 started treatment. 1 completed the trial per protocol.- Due to small sample size no statistical analysis was performed. |
|---|

Notes: