Clinical trial results:
Open-label safety trial of intravenous neridronic acid in subjects with complex regional pain syndrome (CRPS)

Summary

EudraCT number	2016-001164-11
Trial protocol	DE PL
Global end of trial date	09 January 2019

Results information

Result version number	v1 (current)
This version publication date	21 December 2019
First version publication date	21 December 2019

Trial information

Trial identification

Sponsor protocol code	KF7013-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02972359
WHO universal trial number (UTN)	U1111-1180-8099

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52078
Public contact	Grünenthal Trial Information Desk, Grünenthal GmbH, 49 2415693223, Clinical-Trials@grunenthal.com
Scientific contact	Grünenthal Trial Information Desk, Grünenthal GmbH, 49 2415693223, Clinical-Trials@grunenthal.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	08 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2019
Global end of trial reached?	Yes
Global end of trial date	09 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of neridronic acid in subjects with complex regional pain syndrome.

Protection of trial subjects:

The trial was conducted according to ICH-GCP guidelines, the applicable local laws and regulations, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Regulatory authorities were notified of the trial as required by national regulations, and where necessary relevant authorization was obtained.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	United States: 567
Worldwide total number of subjects	580
EEA total number of subjects	13

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)	531
From 65 to 84 years	49
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial started on 20 December 2016 with the enrollment of the first subject and was completed on 09 January 2019 when the last subject completed the last final examination according to the protocol.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	580
Number of subjects completed	316

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 11
Reason: Number of subjects	Lost to follow-up: 3
Reason: Number of subjects	Other reason: 9
Reason: Number of subjects	Inclusion criteria not met/exclusion criteria met: 241

Period 1

Period 1 title	Neridronic Acid 400 mg (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Neridronic acid 400 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sodium neridronate hemi hydrate for intravenous infusion
Investigational medicinal product code	GRT7013
Other name	Neridronic acid
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

108 mg sodium neridronate hemi hydrate (equivalent to 100 mg neridronic acid) in a total volume of 8 mL was diluted in 500 mL normal saline and administered by slow intravenous infusion (240 minutes [maximum 260 minutes]) on Day 1, Day 4, Day 7, and Day 10, resulting in a total dose of 400 mg neridronic acid.

Number of subjects in period 1[1]	Neridronic acid 400 mg
Started	316
Completed	247
Not completed	69
Adverse event, serious fatal	1

Consent withdrawn by subject	30
Adverse event, non-fatal	4
Other reasons	5
Lost to follow-up	26
Reason missing	1
Lack of efficacy	1
Protocol deviation	1

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: 580 subjects were enrolled (signed an informed consent form), 318 subjects were allocated, but only 316 subjects were treated (2 did not meet inclusion/met exclusion criteria). Baseline characteristics are presented for all treated subjects (Safety Set).

Baseline characteristics

Reporting groups	
Reporting group title	Neridronic Acid 400 mg
Reporting group description:	
Safety Set: 316 subjects with at least 1 administration of investigational medicinal product (IM), including any partial infusion.	

Reporting group values	Neridronic Acid 400 mg	Total	
Number of subjects	316	316	
Age categorical			
Units: Subjects			
Adults (18-64 years)	290	290	
From 65-84 years	26	26	
Age continuous			
Units: years			
arithmetic mean	47.4		
standard deviation	± 13.2	-	
Gender categorical			
Units: Subjects			
Female	237	237	
Male	79	79	
Race			
Units: Subjects			
White	297	297	
American Indian or Alaska Native	3	3	
Asian	4	4	
Black or African American	8	8	
Native Hawaiian or other Pacific Islander	0	0	
Other	1	1	
Multiple	3	3	
Ethnicity			
Units: Subjects			
Ethnicity Hispanic or Latino	16	16	
Not Hispanic or Latino	300	300	
Body mass index (BMI)			
Units: kg/m^2			
arithmetic mean	28.3		
standard deviation	± 7.4	-	
Baseline current pain intensity 11-point NRS			
Measured using an 11-point Numerical rating scale (NRS) by answering the following question: "Please rate your pain by selecting the one number that best describes how much pain you have right now." Scores ranged from 0 (no pain) to 10 (pain as bad as you can imagine), a higher score indicates more pain. Baseline was the score assessed before the first dose of investigational medicinal product (IMP). Measure Analysis Population Description: Full Analysis Set; 1 subject's baseline pain assessment was missing (N=315).			
Units: units on a scale			
arithmetic mean	6.59		
standard deviation	± 1.58	-	

Baseline Pain Interference score of the Brief Pain Inventory (BPI)			
Subjects completed the BPI scale questionnaire, which measures the impact of pain on functioning and well-being. The 7 pain interference items: general activity, walking, work, mood, enjoyment of life, relations with others, and sleep, are each rated on a 0 to 10 scale using a 24-hour recall period, with 0 indicating "does not interfere" and 10 indicating "completely interferes". The total Pain Interference Score is calculated by adding the scores for the 7 questions and dividing by 7. For 20 subjects, baseline pain assessments were missing . Full Analysis Set (N=296)			
Units: units on a scale			
arithmetic mean	7.3		
standard deviation	± 1.75	-	

End points

End points reporting groups

Reporting group title	Neridronic acid 400 mg

Reporting group description: -

Primary: Number of Subjects with Occurrence of Any Treatment Emergent Adverse Event (TEAE)

End point title	Number of Subjects with Occurrence of Any Treatment Emergent Adverse Event (TEAE)[1]

End point description:

The primary endpoint of this trial was a binary endpoint assessing whether or not a subject experienced any TEAE.

End point type	Primary

End point timeframe:

Day 1 to Week 52

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: Safety data were summarized descriptively only for the single treatment group neridronic acid 400 mg.

End point values	Neridronic acid 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	316[2]			
Units: Subjects				
Subjects with TEAE	277			
Subjects with serious TEAE	27			
Subjects with non-serious TEAE	275			
Subjects with unexpected TEAE	267			
Subjects with related TEAE	190			
Subjects with related serious TEAE	3			
Subjects with TEAE leading to IMP discont.	12			
Subjects with TEAE leading to trial discont.	6			
Subjects with fatal TEAE	1			

Notes:

[2] - Safety Set: 316 subjects with at least 1 administration of IMP, including any partial infusion.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Occurrence of Permanent Discontinuation From Treatment Due to an Adverse Event

End point title	Number of Subjects with Occurrence of Permanent Discontinuation From Treatment Due to an Adverse Event

End point description:

The investigator could choose to permanently discontinue a subject from treatment if continued

exposure of the subject to neridronic acid could have posed an undue risk to the subject.

End point type	Secondary

End point timeframe:

Day 1 to Day 10

End point values	Neridronic acid 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	316[3]			
Units: Subjects	12			

Notes:

[3] - Safety Set: 316 subjects with at least 1 administration of IMP, including any partial infusion.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Current Pain Intensity Score

End point title	Change From Baseline in the Current Pain Intensity Score

End point description:

The current Complex Regional Pain Syndrome (CRPS)-related pain intensity score was captured at each visit using an 11-point numerical rating scale where 0 = "no pain" and 10 = "pain as bad as you can imagine", a higher score indicates more pain.

End point type	Secondary

End point timeframe:

Baseline to Week 12 and Week 26

End point values	Neridronic acid 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	316[4]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline to Week 12 (N=283)	-1.54 (± 2.27)			
Baseline to Week 26 (N=269)	-1.57 (± 2.45)			

Notes:

[4] - Full Analysis Set (coincided with Safety Set)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Response to Treatment, Defined as at Least 30% Decrease From Baseline in the Current Pain Intensity Score

End point title	Number of Subjects with Response to Treatment, Defined as at Least 30% Decrease From Baseline in the Current Pain Intensity Score

End point description:

Subjects with at least a 30 percent decrease in the current pain intensity score were considered to have responded to treatment.

End point type	Secondary

End point timeframe:

Baseline, at Week 12 and Week 26

End point values	Neridronic acid 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	316[5]			
Units: Subjects				
At least 30% pain reduction - Week 12	105			
At least 30% pain reduction - Week 26	110			

Notes:

[5] - Full Analysis Set (coincided with Safety Set)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Response to Treatment, Defined as at Least 50% Decrease From Baseline in the Current Pain Intensity Score

End point title	Number of Subjects with Response to Treatment, Defined as at Least 50% Decrease From Baseline in the Current Pain Intensity Score

End point description:

Subjects with at least a 50 percent decrease in the current pain intensity score were considered to have responded to treatment.

End point type	Secondary

End point timeframe:

Baseline, at Week 12 and Week 26

End point values	Neridronic acid 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	316[6]			
Units: Subjects				
At least 50% pain reduction - Week 12	75			
At least 50% pain reduction - Week 26	74			

Notes:

[6] - Full Analysis Set (coincided with Safety Set)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change (PGIC) at Week 12

End point title	Patient Global Impression of Change (PGIC) at Week 12

End point description:

The Patient Global Impression of Change (PGIC) is a self-reported measure of perceived change in overall condition since the start of the study. Subjects selected one of seven responses ranging from "very much improved" to "very much worse". A response of "very much improved" or "much improved" is generally regarded as a clinically important improvement.

Overall, 286 out of 316 subjects attended the visit at Week 12 and were asked to complete the PGIC questionnaire.

End point type	Secondary

End point timeframe:

at Week 12

End point values	Neridronic acid 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	286[7]			
Units: Subjects				
Very Much Improved	31			
Much Improved	71			
Minimally Improved	98			
No Change	45			
Minimally Worse	23			
Much Worse	12			
Very Much Worse	3			
Missing	3			

Notes:

[7] - Full Analysis Set (coincided with Safety Set)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change (PGIC) at Week 26

End point title	Patient Global Impression of Change (PGIC) at Week 26

End point description:

The Patient Global Impression of Change (PGIC) is a self-reported measure of perceived change in overall condition since the start of the study. Subjects selected one of seven responses ranging from "very much improved" to "very much worse". A response of "very much improved" or "much improved" is generally regarded as a clinically important improvement.

Overall, 273 out of 316 subjects attended the visit at Week 26 and were asked to complete the PGIC questionnaire.

End point type	Secondary

End point timeframe:

at Week 26

End point values	Neridronic acid 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	273[8]			
Units: Subjects				
Very Much Improved	38			
Much Improved	58			
Minimally Improved	84			
No Change	52			
Minimally Worse	25			
Much Worse	10			
Very Much Worse	2			
Missing	4			

Notes:

[8] - Full Analysis Set (coincided with Safety Set)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Pain Interference Score of the Brief Pain Inventory (BPI)

End point title	Change in the Pain Interference Score of the Brief Pain Inventory (BPI)

End point description:

The Brief Pain Inventory (BPI) Interference Score is the mean value of 7 self-reported items in question 9 of the BPI Short Form Questionnaire. Subjects rated their interference of pain with general activity, walking, work, sleep and other activities in the past 24 hours, with possible ratings from 0 (does not interfere) to 10 (completely interferes). The BPI interference Score ranges from 0 to 10, with higher values indicating greater pain interference of daily activities.

End point type	Secondary

End point timeframe:

Baseline to Week 12 and Week 26

End point values	Neridronic acid 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	316[9]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline to Week 12 (N=264)	-2.2 (± 2.49)			
Baseline to Week 26 (N=251)	-2.1 (± 2.64)			

Notes:

[9] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Week 52

Adverse event reporting additional description:

Subjects were questioned about possible adverse events (AEs) with non-leading questions before administration of IMP and at regular intervals thereafter. All AEs reported spontaneously by subjects at any time point were also documented.
Overall, 316 of 318 allocated subjects were treated (Safety Set). Treatment emergent AEs are tabulated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Neridronic acid 400 mg

Reporting group description:

Safety Set: 316 subjects with at least 1 administration of investigational medicinal product (IMP), including any partial infusion.

Serious adverse events	Neridronic acid 400 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 316 (8.54%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 316 (0.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Procedural pain			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Myocardial infarction			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stress cardiomyopathy			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Leg amputation			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 316 (0.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 316 (0.63%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Condition aggravated			

subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver disorder			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			

subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	2 / 316 (0.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	2 / 316 (0.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Rotator cuff syndrome			
subjects affected / exposed	1 / 316 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 316 (0.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Neridronic acid 400 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	275 / 316 (87.03%)		
Nervous system disorders			
Headache			

subjects affected / exposed	65 / 316 (20.57%)		
occurrences (all)	96		
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	30 / 316 (9.49%)		
occurrences (all)	44		
Fatigue			
subjects affected / exposed	32 / 316 (10.13%)		
occurrences (all)	39		
Pain			
subjects affected / exposed	28 / 316 (8.86%)		
occurrences (all)	37		
Pyrexia			
subjects affected / exposed	18 / 316 (5.70%)		
occurrences (all)	19		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	34 / 316 (10.76%)		
occurrences (all)	46		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	27 / 316 (8.54%)		
occurrences (all)	31		
Back pain			
subjects affected / exposed	25 / 316 (7.91%)		
occurrences (all)	30		
Bone pain			
subjects affected / exposed	17 / 316 (5.38%)		
occurrences (all)	20		
Myalgia			
subjects affected / exposed	52 / 316 (16.46%)		
occurrences (all)	70		
Pain in extremity			
subjects affected / exposed	25 / 316 (7.91%)		
occurrences (all)	30		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2016	Amendment 01 This amendment was implemented to: • Remove the requirement for blood sampling for a population pharmacokinetic analysis. A population pharmacokinetic analysis of the cumulative dose of 400 mg was not required because sufficient data had been collected in a previous trial. • Follow-up all subjects for up to 52 weeks. • Add continuous real-time ECG monitoring covering the period of infusions. • Modify the allowance of medications known to prolong the QT interval.
20 March 2017	Amendment 02 (valid for Germany) This amendment was implemented to: • Exclude subjects who were taking forbidden concomitant medications/therapies or were not able to follow the rules for use of concomitant medications/treatments. • Revise the dose rationale to include additional information from a previous pilot study. • State that treatment discontinuation was to be permanent if eye symptoms reoccurred. • Clarify the distribution of ampules and vials during the trial.
19 April 2017	Amendment 03 (valid for all countries) This amendment was implemented to: • Apply all changes introduced in protocol amendment 02 to all countries. • Clarify that Visit 1 did not need to be performed in a fasted state. • Adjust the duration of stable contraceptive use from 2 months to 1 month prior to allocation. • Allow repeat testing of estimated glomerular filtration rate (eGFR), albumine creatinine ratio (ACR), serum calcium or magnesium, and vitamin D level. • Clarify that the combination of opioids and benzodiazepines was forbidden only if the combination was felt to jeopardize subject safety, in the opinion of the investigator. • Introduce re-enrollment of suitably qualified subjects who failed allocation due to technical reasons. • Clarify that drugs of abuse testing was to be performed at the site and that the investigator should judge whether subjects who were receiving stable doses of prescribed medications containing amphetamines, benzodiazepines, or opioids could participate (together with approval by the sponsor). • Exclude subjects incapable of signing the informed consent. • Only include subjects who had failed at least 2 available treatments for CRPS, 1 of which had to be a pharmacologic treatment. • Adjust exclusion criterion for urinary ACR from <30 mg/g to <150 mg/g, due to impact on enrollment of subjects with moderate levels of urinary albumin and based on lack of evidence for changes in urinary ACR in a previous trial. • Adjust temporary IMP discontinuation criteria to allow resumption of treatment if urinary ACR was <150 mg/g, and remove temporary discontinuation criterion for eGFR <50 mL/min/1.73 m2 and urinary ACR >150 mg/g. A persistent change of this magnitude remained a criterion for permanent discontinuation. • Adapt time period for collection of dental history. • Clarify that the Pharmacodynamics Set included only subjects who had been treated. • Clarify requirements for documentation of abnormal laboratory values
17 November 2017	Amendment 04 (valid for United States) This amendment was implemented to: • Increase the size of the target population. • Clarify the planned number of bone biopsies and bone densitometry and MRI assessments.

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.

Due to the open-label, uncontrolled nature of the trial and the concomitant use of pain medication, the effect of neridronic acid on pain intensity and the side effect profile of neridronic acid have to be interpreted with care.

Notes: