Clinical trial results:
Randomized, double-blind, placebo-controlled trial investigating the efficacy and safety of intravenous neridronic acid in subjects with complex regional pain syndrome (CRPS)

Summary

EudraCT number	2016-003833-91
Trial protocol	ES
Global end of trial date	31 July 2019

Results information

Result version number	v1 (current)
This version publication date	25 July 2020
First version publication date	25 July 2020

Trial information

Trial identification

Sponsor protocol code	KF7013-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03530345
WHO universal trial number (UTN)	U1111-1187-8036

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstraße 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	11 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2019
Global end of trial reached?	Yes
Global end of trial date	31 July 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superior efficacy of a cumulative dose of 400 mg intravenous neridronic acid versus placebo for the treatment of CRPS-related pain.

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	30 May 2018
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	Spain: 20
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United States: 141
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Korea, Republic of: 7
Worldwide total number of subjects	182
EEA total number of subjects	24

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)	170
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first subject was enrolled on 30 May 2018, the last subject's last assessment was on 31 July 2019. After a pooled interim analysis of primary endpoint data of trials KF7013-02 and KF7013-04, recruitment was stopped as interim results indicated futility (neridronic acid unlikely to be statistically significantly superior to placebo).

Pre-assignment

Screening details:

182 subjects were enrolled (signed consent), 57 were allocated to treatment and received neridronate or placebo. Of 125 subjects not allocated, 95 did not meet inclusion/met exclusion criteria, 1 was lost to follow-up, 9 withdrew consent, 1 had technical problems, and 19 were not allocated for other reasons (mainly trial termination).

Period 1

Period 1 title	Treatment Period A/Follow-up Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Assessor, Subject

Blinding implementation details:

Blinded treatment with neridronic acid or placebo in Treatment Period A.

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline to Week 26: Neridronic Acid TPA

Arm description:

Neridronic acid 400 mg administered in Treatment Period A (TPA) by 4 intravenous infusions within 10 Days; Follow-up Period 1 until 26 weeks.

Arm type	Experimental
Investigational medicinal product name	Neridronate acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Neridronic acid 400 mg administered by 4 intravenous infusions within 10 Days.

Arm title	Baseline to Week 26: Placebo TPA

Arm description:

Matching placebo was administered in Treatment Period A (TPA) by 4 intravenous infusions within 10 Days; Follow-up Period 1 until 26 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Matching placebo was administered by 4 intravenous infusions within 10 Days.

Number of subjects in period 1[1]	Baseline to Week 26: Neridronic Acid TPA	Baseline to Week 26: Placebo TPA
Started	28	29
Treatment Period A completers	26	27
Follow-up Period 1 completers	7	7
Completed	7	7
Not completed	21	22
Various reasons (mainly trial termination)	21	22

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: 182 subjects were enrolled (signed consent), 57 were allocated to treatment and received trial medication. Baseline characteristics are reported for subjects who received trial medication.

Period 2

Period 2 title	Treatment Period B/Follow-up Period 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Week 26-52: Neridronic acid TPA, Neridronic acid TPB

Arm description:

Subjects with neridronic acid treatment in Treatment Period A (TPA) who received neridronic acid 100 mg - 4 intravenous infusions within 10 days also in Treatment Period B (TPB) with a Follow-up Period 2 until 52 weeks. Infusions in Treament Period B were not blinded.

Arm type	Experimental
Investigational medicinal product name	Neridronate acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Neridronic acid 400 mg administered by 4 intravenous infusions within 10 Days (open-label infusions)

Arm title	Week 26-52: Placebo TPA, Neridronic acid TPB

Arm description:

Subjects with placebo treatment in Treatment Period A (TPA) who received neridronic acid 100 mg - 4 intravenous infusions within 10 days in Treatment Period B (TPB) with a Follow-up Period 2 until 52 weeks. Infusions in Treament Period B were not blinded.

Arm type	Experimental
Investigational medicinal product name	Neridronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Neridronic acid 400 mg administered by 4 intravenous infusions within 10 Days.

Arm title	Week 26 to Week 52: Neridronic Acid TPA

Arm description:

Subjects who had completed treatment with neridronic acid treatment in Treatment Period A/Follow-up Period 1 were followed up without administration of trial medication until 52 weeks in Follow-up Period 2.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Week 26-52: Neridronic acid TPA, Neridronic acid TPB	Week 26-52: Placebo TPA, Neridronic acid TPB	Week 26 to Week 52: Neridronic Acid TPA
Started	5	7	2
Treatment Period B completers	4	6	0
Follow-up Period 2 completers	0	0	0
Completed	0	0	0
Not completed	5	7	2
Discontinued before end of Follow-up Period 2	5	7	-
Various reasons (mainly trial termination)	-	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Baseline to Week 26: Neridronic Acid TPA
Reporting group description:	
Neridronic acid 400 mg administered in Treatment Period A (TPA) by 4 intravenous infusions within 10 Days; Follow-up Period 1 until 26 weeks.	
Reporting group title	Baseline to Week 26: Placebo TPA
Reporting group description:	
Matching placebo was administered in Treatment Period A (TPA) by 4 intravenous infusions within 10 Days; Follow-up Period 1 until 26 weeks.	

Reporting group values	Baseline to Week 26: Neridronic Acid TPA	Baseline to Week 26: Placebo TPA	Total
Number of subjects	28	29	57
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	28	25	53
From 65-84 years	0	4	4
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	46.1	49.4	
standard deviation	± 11.0	± 12.1	-
Gender categorical Units: Subjects			
Female	22	22	44
Male	6	7	13
Race Units: Subjects			
American Indian or Alska Native	0	0	0
Asian	2	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	1	3
White	24	28	52
More than one race	0	0	0
Unknown or Not Reported	0	0	0
CRPS type			
CRPS Type I: Occurs after a minor or major tissue injury without clinical signs of major peripheral nerve injury. CRPS Type II: Occurs after an injury with clinical signs of major peripheral nerve injury.			
Units: Subjects			

Type I	25	21	46
Type II	3	8	11
Unknown	0	0	0
Time since onset of CRPS symptoms			
Units: months			
median	17.72	13.47	
inter-quartile range (Q1-Q3)	7.60 to 22.02	8.20 to 18.87	-
Time since diagnosis of CRPS			
Units: months			
median	9.15	11.37	
inter-quartile range (Q1-Q3)	4.82 to 16.07	3.30 to 17.87	-

End points

End points reporting groups

Reporting group title	Baseline to Week 26: Neridronic Acid TPA
Reporting group description:	
Neridronic acid 400 mg administered in Treatment Period A (TPA) by 4 intravenous infusions within 10 Days; Follow-up Period 1 until 26 weeks.	
Reporting group title	Baseline to Week 26: Placebo TPA
Reporting group description:	
Matching placebo was administered in Treatment Period A (TPA) by 4 intravenous infusions within 10 Days; Follow-up Period 1 until 26 weeks.	
Reporting group title	Week 26-52: Neridronic acid TPA, Neridronic acid TPB
Reporting group description:	
Subjects with neridronic acid treatment in Treatment Period A (TPA) who received neridronic acid 100 mg - 4 intravenous infusions within 10 days also in Treatment Period B (TPB) with a Follow-up Period 2 until 52 weeks. Infusions in Treament Period B were not blinded.	
Reporting group title	Week 26-52: Placebo TPA, Neridronic acid TPB
Reporting group description:	
Subjects with placebo treatment in Treatment Period A (TPA) who received neridronic acid 100 mg - 4 intravenous infusions within 10 days in Treatment Period B (TPB) with a Follow-up Period 2 until 52 weeks. Infusions in Treament Period B were not blinded.	
Reporting group title	Week 26 to Week 52: Neridronic Acid TPA
Reporting group description:	
Subjects who had completed treatment with neridronic acid treatment in Treatment Period A/Follow-up Period 1 were followed up without administration of trial medication until 52 weeks in Follow-up Period 2.	

Primary: Change From Baseline to Week 12 in the Average Pain Intensity Score (Weekly Average of Pain Values Recorded Daily in the Electronic Diary)

End point title	Change From Baseline to Week 12 in the Average Pain Intensity Score (Weekly Average of Pain Values Recorded Daily in the Electronic Diary)
End point description:	
In the Baseline Phase and in Treatment Period A/Follow-up Period 1, subjects were asked to assessed their average CRPS-related pain on an 11-point numerical rating scale (NRS) - from 0 = "no pain" to 10 = "pain as bad as you can imagine" and report it once daily (in the evening, 24-hour recall) in an electronic diary. Changes from baseline (average for the Baseline Phase) to the weekly average for Week 12 were calculated for the Full Analysis Set, i.e., all subjects treated in Treatment Period A with all data available at the time of last subject out following premature trial termination.	
End point type	Primary
End point timeframe:	
From the Baseline Phase (Day -7 to Day -1) to Week 12	

End point values	Baseline to Week 26: Neridronic Acid TPA	Baseline to Week 26: Placebo TPA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: Units on a scale				

least squares mean (standard error)	-1.23 (± 0.310)	-0.16 (± 0.305)		

Statistical analyses

Statistical analysis title	Superiority testing

Statistical analysis description:

Mixed-effects model for repeated measures (MMRM) defined with baseline pain intensity as covariate, the factors geographic region, week, treatment and treatment-by-week as fixed effects, and an unstructured covariance matrix to model the covariance structure of the repeated measurements.

Comparison groups	Baseline to Week 26: Placebo TPA v Baseline to Week 26: Neridronic Acid TPA
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0111 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.89
upper limit	-0.26
Variability estimate	Standard error of the mean
Dispersion value	0.404

Notes:

[1] - Two-sided p-value for testing superiority of neridronic acid 400 mg compared to placebo.

Secondary: Change From Baseline to Week 26 in the Average Pain Intensity Recorded on the Tablet Computer

End point title	Change From Baseline to Week 26 in the Average Pain Intensity Recorded on the Tablet Computer

End point description:

11-point NRS - from 0 = "no pain" to 10 = "pain as bad as you can imagine" - reported at the visits on a tablet computer (24-hour recall). Changes from baseline to Week 26 were planned to be analyzed.

Secondary endpoints were not analyzed because the trial was terminated prematurely following a pooled interim analysis of primary endpoint data of trials KF7013-02 and KF7013-04 (EudraCT 2017-004244-37).

End point type	Secondary

End point timeframe:

From baseline (Visit 2 [Day 1]) to Visit 11 (Week 26).

End point values	Baseline to Week 26: Neridronic Acid TPA	Baseline to Week 26: Placebo TPA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[2] - No analysis performed

[3] - No analysis performed

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Response to Treatment, Defined as at Least 30% Decrease from Baseline in the Average Pain Intensity at Week 12, Recorded on the Tablet Computer

End point title	Pain Response to Treatment, Defined as at Least 30% Decrease from Baseline in the Average Pain Intensity at Week 12, Recorded on the Tablet Computer

End point description:

11-point NRS - from 0 = "no pain" to 10 = "pain as bad as you can imagine" - reported at the visits on a tablet computer (24-hour recall).
The number of subjects with response at Week 12 was planned to be determined.

Secondary endpoints were not analyzed because the trial was terminated prematurely following a pooled interim analysis of primary endpoint data of trials KF7013-02 and KF7013-04 (EudraCT 2017-004244-37).

End point type	Secondary

End point timeframe:

From baseline (Visit 2 [Day 1]) to Visit 8 (Week 12)

End point values	Baseline to Week 26: Neridronic Acid TPA	Baseline to Week 26: Placebo TPA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Number of subjects				

Notes:

[4] - No analysis performed.

[5] - No analysis performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Response to Treatment, Defined as at Least 30% Decrease from Baseline in the Average Pain Intensity at Week 26, Recorded on the Tablet Computer

End point title	Pain Response to Treatment, Defined as at Least 30% Decrease from Baseline in the Average Pain Intensity at Week

	26, Recorded on the Tablet Computer

End point description:

11-point NRS - from 0 = "no pain" to 10 = "pain as bad as you can imagine" - reported at the visits on a tablet computer (24-hour recall).
The number of subjects with response at Week 26 was planned to be determined.

Secondary endpoints were not analyzed because the trial was terminated prematurely following a pooled interim analysis of primary endpoint data of trials KF7013-02 and KF7013-04 (EudraCT 2017-004244-37).

End point type	Secondary

End point timeframe:

From baseline (Visit 2 [Day 1]) to Visit 11 (Week 26)

End point values	Baseline to Week 26: Neridronic Acid TPA	Baseline to Week 26: Placebo TPA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Number of subjects				

Notes:

[6] - No analysis performed.

[7] - No analysis performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in the Pain Intensity Level of Dynamic Mechanical Allodynia (DMA)

End point title	Change From Baseline to Week 12 in the Pain Intensity Level of Dynamic Mechanical Allodynia (DMA)

End point description:

Dynamic Mechanical Allodynia: a Tactile Stimulus is Applied in a Single Sweeping Motion (1 cm to 2 cm Length) on the Skin on the Affected Limb. The subjects were asked to judge the stimulus intensity by means of an NRS (0 to 10). "0" in this case means "no pain". Each "pricking", "stinging" or "burning" sensation is defined as a painful sensation, which should always be evaluated by giving a value greater than "0". "10" corresponds to the individual maximum pain imaginable. Changes from baseline to Week 12 were planned to be analyzed.

Secondary endpoints were not analyzed because the trial was terminated prematurely following a pooled interim analysis of primary endpoint data of trials KF7013-02 and KF7013-04 (EudraCT 2017-004244-37).

End point type	Secondary

End point timeframe:

From baseline (Visit 2 [Day 1]) to Visit 8 (Week 12)

End point values	Baseline to Week 26: Neridronic Acid TPA	Baseline to Week 26: Placebo TPA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: Units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[8] - No analysis performed.

[9] - No analysis performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in the Pressure Pain Threshold (PPT) Ratio for the Thenar Muscle/Abductor Hallucis Muscle

End point title	Change From Baseline to Week 12 in the Pressure Pain Threshold (PPT) Ratio for the Thenar Muscle/Abductor Hallucis Muscle

End point description:

Pressure pain threshold: using a pressure algometer (contact area 1 cm2), the threshold for pressure-induced pain is measured on the thenar muscle/abductor hallucis muscle in 3 series of slowly increasing stimulus intensities (at a rate of about 50 kPa/s). The threshold is then determined as the arithmetic mean of the 3 series (in kPa).
The ratio of the thresholds of the affected limb versus the unaffected limb was planned to be calculated and used for the determination of the change from baseline.

Secondary endpoints were not analyzed because the trial was terminated prematurely following a pooled interim analysis of primary endpoint data of trials KF7013-02 and KF7013-04 (EudraCT 2017-004244-37).

End point type	Secondary

End point timeframe:

From baseline (Visit 2 [Day 1]) to Visit 8 (Week 12)

End point values	Baseline to Week 26: Neridronic Acid TPA	Baseline to Week 26: Placebo TPA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Ratio				
arithmetic mean (standard deviation)	()	()		

Notes:

[10] - No analysis performed.

[11] - No analysis performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in the Ratio of the Figure of Eight Measurements of the Affected Limb Versus the Unaffected Limb

End point title	Change From Baseline to Week 12 in the Ratio of the Figure of Eight Measurements of the Affected Limb Versus the Unaffected Limb

End point description:

In subjects with the CRPS sign of edema on the CRPS severity score at baseline, circumference of the hand or foot will be measured by the investigator with measurement tape using the figure-of-eight method at both the affected limb and the contralateral unaffected limb. Each measurement will be performed 3 times. The average of the 3 measurements will be used for further analysis. The ratio of the averages of the affected limb versus the unaffected limb was planned to be calculated and used for the determination of the change from baseline.

Secondary endpoints were not analyzed because the trial was terminated prematurely following a pooled interim analysis of primary endpoint data of trials KF7013-02 and KF7013-04 (EudraCT 2017-004244-37).

End point type	Secondary

End point timeframe:

From baseline (Visit 2 [Day 1]) to Visit 8 (Week 12)

End point values	Baseline to Week 26: Neridronic Acid TPA	Baseline to Week 26: Placebo TPA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: Ratio				
arithmetic mean (standard deviation)	()	()		

Notes:

[12] - No analysis performed.

[13] - No analysis performed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were documented from the time of enrollment (i.e., the time the informed consent form was signed) up to the time of the last protocol scheduled contact, i.e., date of last visit/contact (could be a phone call, e.g., in case of withdrawal).

Adverse event reporting additional description:

Only treatment emergent adverse events (TEAEs) reported after first administration of trial medication are reported. Subjects with TEAEs may be presented in 2 of 6 reporting groups depending on the time the TEAEs were reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Baseline to Week 26: Neridronic Acid TPA

Reporting group description:

In Treatment Period A (TPA), subjects received neridronic acid 100 mg - 4 intravenous infusions within 10 Days; Follow-up Period 1 until 26 weeks.

Reporting group title	Baseline to Week 26: Placebo TPA

Reporting group description:

In Treatment Period A (TPA), subjects received matching placebo - 4 intravenous infusions within 10 days; Follow-up Period 1 until 26 weeks.

Reporting group title	Week 26 to Week 52: Placebo TPA

Reporting group description:

Subjects with placebo treatment in Treatment Period A/Follow-up Period 1 were followed up without administration of trial medication until 52 weeks in Follow-up Period 2.

Reporting group title	Week 26 to Week 52: Placebo TPA, Neridronic Acid TPB

Reporting group description:

Subjects who had completed treatment with placebo in Treatment Period A/Follow-up Period 1 received neridronic acid treatment (100 mg - 4 intravenous infusions within 10 days) in Treatment Period B (TPB) with a Follow-up Period 2 until 52 weeks.

Reporting group title	Week 26 to Week 52: Neridronic Acid TPA

Reporting group description:

Subjects who had completed treatment with neridronic acid treatment in Treatment Period A/Follow-up Period 1 were followed up without administration of trial medication until 52 weeks in Follow-up Period 2.

Reporting group title	Week 26 to Week 52: Neridronic Acid TPA, Neridronic Acid TPB

Reporting group description:

Subjects who had completed treatment with neridronic acid in Treatment Period A/Follow-up Period 1 received re-treatment with neridronic acid 100 mg - 4 intravenous infusions within 10 days in Treatment Period B (TPB) with a Follow-up Period 2 until 52 weeks.

Serious adverse events	Baseline to Week 26: Neridronic Acid TPA	Baseline to Week 26: Placebo TPA	Week 26 to Week 52: Placebo TPA
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 28 (7.14%)	0 / 29 (0.00%)	0 / 22 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Week 26 to Week 52: Placebo TPA, Neridronic Acid TPB	Week 26 to Week 52: Neridronic Acid TPA	Week 26 to Week 52: Neridronic Acid TPA, Neridronic Acid TPB
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Baseline to Week 26: Neridronic Acid TPA	Baseline to Week 26: Placebo TPA	Week 26 to Week 52: Placebo TPA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 28 (57.14%)	15 / 29 (51.72%)	0 / 22 (0.00%)
Surgical and medical procedures			
Foot operation			

subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Medical device removal			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Medical device implantation			
subjects affected / exposed	0 / 28 (0.00%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Acute phase reaction			
subjects affected / exposed	4 / 28 (14.29%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	7	0	0
Chest pain			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	1 / 28 (3.57%)	2 / 29 (6.90%)	0 / 22 (0.00%)
occurrences (all)	1	5	0
Feeling cold			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	1 / 28 (3.57%)	2 / 29 (6.90%)	0 / 22 (0.00%)
occurrences (all)	1	2	0
Oedema peripheral			
subjects affected / exposed	2 / 28 (7.14%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	5	0	0
Pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Pulmonary embolism			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Lipase increased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Epicondylitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Skin laceration			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	0 / 28 (0.00%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial flutter			

subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 28 (7.14%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	2 / 28 (7.14%)	3 / 29 (10.34%)	0 / 22 (0.00%)
occurrences (all)	2	6	0
Migraine			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Occipital neuralgia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Eye pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Burning mouth syndrome			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Dental paraesthesia			

subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	2 / 28 (7.14%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	2	1	0
Gastritis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Gingival discomfort			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 28 (7.14%)	4 / 29 (13.79%)	0 / 22 (0.00%)
occurrences (all)	2	4	0
Vomiting			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Joint instability			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			
subjects affected / exposed	1 / 28 (3.57%)	2 / 29 (6.90%)	0 / 22 (0.00%)
occurrences (all)	1	2	0
Periarthritis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Synovitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	2 / 28 (7.14%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Pharyngitis streptococcal			

subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 29 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	0 / 22 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Week 26 to Week 52: Placebo TPA, Neridronic Acid TPB	Week 26 to Week 52: Neridronic Acid TPA	Week 26 to Week 52: Neridronic Acid TPA, Neridronic Acid TPB
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	1 / 23 (4.35%)	0 / 5 (0.00%)
Surgical and medical procedures			
Foot operation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Medical device removal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Medical device implantation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 23 (4.35%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Acute phase reaction			
subjects affected / exposed	3 / 7 (42.86%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	6	0	0
Chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Fatigue			

subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Feeling cold			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Investigations			

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Epicondylitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin laceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	1 / 7 (14.29%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Occipital neuralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Eye disorders			
Dry eye			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Burning mouth syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dental paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gingival discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vomiting			

subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Joint instability			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Periarthritis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Synovitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 23 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2018	The principal changes in this amendment are based on FDA feedback received in September 2018 as well as feedback from ECs, IRBs, and other regulatory authorities. The following changes were implemented: • Addition of weekly pain intensity assessments after Week 12 using an electronic diary. • Clarification of concomitant analgesic medication use as a (non-objective related) outcome. • Simplification of the description of "other data to be collected that are not directly attributed to or considered as an endpoint" (there was no change to the planned assessments or evaluations). • Removal of specification of male contraception in inclusion criterion 6. • Clarification in exclusion criterion 1 that the quoted eGFR and ACR thresholds refer to severe renal impairment. refer to severe renal impairment.

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.

A protocol specified interim analysis was conducted on pooled primary endpoint data of trials KF7013-02 and KF7013-04. The interim analysis indicated futility and both trials were stopped.

Notes: