# 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<br>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<br>Units: years | | | |
| arithmetic mean | 46.1 | 49.4 | |
| standard deviation | ± 11.0 | ± 12.1 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 22 | 22 | 44 |
| Male | 6 | 7 | 13 |
| Race<br>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.<br>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:<br>• Addition of weekly pain intensity assessments after Week 12 using an electronic diary.<br>• Clarification of concomitant analgesic medication use as a (non-objective related) outcome.<br>• 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).<br>• Removal of specification of male contraception in inclusion criterion 6.<br>• Clarification in exclusion criterion 1 that the quoted eGFR and ACR thresholds refer to severe renal impairment.<br>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: