SDR-CTR-SYN-06

Trial code	KF7013-04
Title of trial	Placebo-controlled efficacy and safety trial of intravenous neridronic acid in subjects with complex regional pain syndrome (CRPS)
Trial design	Parallel-group, double-blind, randomized, placebo-controlled trial with 2 treatment periods (Treatment Period A and Treatment Period B)
Development phase	Phase III
EudraCT number	2017-004244-37 IND number 115811 (US sites only)
Universal Trial Number:	U1111-1203-5020
Investigational medicinal products	Neridronic acid, placebo
Indication	Treatment of CRPS
International coordinating investigator	[redacted], MD c/o Northwest Clinical Research Center, 1951 152nd Place NE, Suite 200, Bellevue, WA 98007, USA
Trial sites	Canada (6 sites), Czechia (3 sites), Poland (3 sites), Serbia (4 sites), Slovakia (4 sites), United Kingdom (10 sites), United States (41 sites)
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Sponsor's signatory	[redacted], MD, Medical Lead Contact number: +49 (0) 241-569-0
Trial period	First subject in: 31 May 2018 Last subject out: 01 Aug 2019

Objectives

The planned objectives of the trial were:

Objective	Endpoint/Outcome	Measure description and timeframe
Primary To demonstrate the superior efficacy of a cumulative dose of 400 mg intravenous neridronic acid versus placebo for the treatment of CRPS-related pain.	**Primary** Change from baseline to Week 12 in the average pain intensity score (weekly average of pain values recorded daily in the electronic diary).	**Primary** 11-point numerical rating scale (NRS)—from 0 = "no pain" to 10 = "pain as bad as you can imagine" —reported once daily (in the evening, 24-hour recall) in an electronic diary. The change from the baseline phase (Day -7 to Day -1) to Week 12 will be analyzed.

Objective	Endpoint/Outcome	Measure description and timeframe
Secondary	**Secondary**	**Secondary**
To assess the efficacy of a cumulative dose of 400 mg intravenous neridronic acid versus placebo for the treatment of CRPS-related pain.	Change from baseline to Week 26 in the average pain intensity recorded on the tablet computer.	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 change from baseline (Visit 2 [Day 1]) to Visit 11 (Week 26) will be analyzed.
	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.	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 change from baseline (Visit 2 [Day 1]) to Visit 8 (Week 12) will be analyzed.
	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.	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 change from baseline (Visit 2 [Day 1]) to Visit 11 (Week 26) will be analyzed.
Secondary	**Secondary**	**Secondary**
To assess the efficacy of a cumulative dose of 400 mg intravenous neridronic acid versus placebo on the dynamic mechanical allodynia (DMA).	Change from baseline to Week 12 in the pain intensity level of DMA.	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 are 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. The change from baseline (Visit 2 [Day 1]) to Visit 8 (Week 12) will be analyzed.
To assess the efficacy of a cumulative dose of 400 mg intravenous neridronic acid versus placebo on the pressure pain threshold (PPT).	Change from baseline to Week 12 in the PPT ratio for the thenar muscle/abductor hallucis muscle.	Pressure pain threshold: using a pressure algometer (contact area 1 cm^2), 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 will be calculated. The change from baseline (Visit 2 [Day 1]) to Visit 8 (Week 12) will be analyzed.

Objective	Endpoint/Outcome	Measure description and timeframe
To assess the efficacy of a cumulative dose of 400 mg intravenous neridronic acid versus placebo on edema of the hand or foot.	Change from baseline to Week 12 in the ratio of the figure of eight measurements of the affected limb versus the unaffected limb.	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 will be calculated. The change from baseline (Visit 2 [Day 1]) to Visit 8 (Week 12) will be analyzed.

Investigational medicinal products (IMP)

108 mg sodium neridronate hemi hydrate (equivalent to 100 mg neridronic acid) in a total volume of 8 mL; batch number: P56007A; expiration date: Feb 2020.

Matching placebo (excipients) in a total volume of 8 mL. Batch numbers: P56006P and P56008P; expiration dates: Aug 2021 and Jun 2023.

Trial treatments

For subjects with no or mild renal impairment, the full contents of a single vial (8 mL) was diluted in 500 mL normal saline and administered by slow intravenous infusion (240 minutes [maximum 260 minutes]) 4 times over a period of approximately 10 days (at Visit 2, Visit 3, Visit 4, and Visit 5), resulting in a total dose of 400 mg neridronic acid or matching placebo.

For subjects with no or mild renal impairment included in Treatment Period B at Week 26, the full contents of a single vial (8 mL) was diluted in 500 mL normal saline and administered by slow intravenous infusion (240 minutes [maximum 260 minutes]) 4 times over a period of approximately 10 days (at Visit 11, Visit 12, Visit 13, and Visit 14), resulting in a total dose of 400 mg neridronic acid.

For subjects with moderate renal impairment, the following dose adjustments were applicable:

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Stage 3a (estimated glomerular filtration rate [eGFR] 45 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2)

6 mL of solution from a single vial (corresponding to neridronic acid 75 mg) were diluted in 500 mL normal saline and administered by slow intravenous infusion (240 minutes [maximum 260 minutes]) at each treatment visit, resulting in a total dose of 300 mg neridronic acid or matching placebo.

CKD-EPI Stage 3b (eGFR 30 mL/min/1.73 m^2 to <45 mL/min/1.73 m^2)

5 mL of solution from a single vial (corresponding to neridronic acid 62.5 mg) were diluted in 500 mL normal saline and administered by slow intravenous infusion (240 minutes [maximum 260 minutes]) at each treatment visit, resulting in a total dose of 250 mg neridronic acid or matching placebo.

Trial population

The trial included male or female subjects who were at least 18 years of age with a confirmed diagnosis of CRPS (Type I [CRPS-I] or Type II [CRPS-II]) according to the clinical diagnostic criteria recommended by the International Association for the Study of Pain (IASP; "Budapest clinical criteria") at Visit 1. Signs and symptoms of CRPS had to apply to an affected limb (arm or leg) and had to demonstrate asymmetry with respect to the contralateral limb. The CRPS duration had to be 2 years or less since onset of symptoms. Subjects were required to have a baseline average pain intensity score of greater than or equal to 4 using an 11-point NRS, referring to the CRPS-affected limb (average of pain recorded over 7 days).

Subjects had to be on a stable treatment regimen for CRPS for at least 1 month prior to allocation. Subjects had to have failed attempts with at least 2 available treatments for CRPS, 1 of which had to be a pharmacologic treatment.

Subjects with evidence of severe renal impairment (eGFR less than 30 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine equation) or a urinary albumin creatinine ratio (ACR) greater than 150 mg/g were excluded.

Summary of the trial procedures and assessments

There was an Enrollment Period lasting up to 60 days, a Treatment Period A consisting of 4 infusions over 10 days, and a Follow-up Period 1 from Visit 6 (Week 2) up until Visit 11 (Week 26).

At Visit 11, subjects not meeting the pre-specified criteria to continue into Treatment Period B continued in Follow-up Period 2 until Visit 17 (Week 52). Subjects meeting the pre-specified criteria entered the open-label Treatment Period B with 4 additional infusions over 10 days and follow-up visits until Visit 17 (Week 52).

At the Enrollment Visit, the trial objectives, procedures, and risks were explained to the subject and the informed consent form was signed. Medical history was obtained, a physical examination was conducted, and other safety assessments were performed. Signs and symptoms of CRPS were assessed to confirm the diagnosis of CRPS according to the Budapest clinical criteria and to provide a baseline for the CRPS severity score. Subjects were trained to report their average, worst, and current pain.

Subject eligibility was further assessed during the enrollment period. Subjects who had not had a recent dental examination were allowed to undergo a dental visit. Calcium and vitamin D supplementation were initiated for all subjects, and if needed, a short course of high dose vitamin D was administered to ensure sufficient vitamin D levels prior to treatment.

Subjects meeting all eligibility criteria received infusions of IMP during visits on Day 1, Day 4, Day 7, and Day 10. Flexibility of ±1 day was allowed for Day 4, Day 7, and Day 10. Infusion visits on consecutive days was not allowed.

Subjects meeting the pre-specified criteria at Visit 11 received infusions of IMP on Day 183, Day 186, Day 189, and Day 192. Flexibility of ±1 day was allowed for Day 186, Day 189, and Day 192. Infusion visits on consecutive days was not allowed.

Subjects were asked to record their average, worst, and current CRPS-related pain intensity once daily in the electronic diary (in the evening), using an 11-point NRS (from 0 = "no pain" to

10 = "pain as bad as you can imagine") starting at Visit 1 and continuing until Visit 8. Worst and average pain intensity were recorded for a 24-hour recall period. After Visit 8 up to Visit 17, subjects were asked to record their average, worst, and current CRPS-related pain intensity once weekly in the electronic diary (in the evening) using the same 11-point NRS and a 24-hour recall period.

Subjects were also asked to record the pain intensity ratings for average, worst, and current CRPS-related pain directly on a tablet computer maintained at the site at Visit 2 and from Visit 7 to Visit 17. Worst and average pain intensity ratings in this case were based on a 24-hour recall period.

During Treatment Period A, Follow-up Period 1, Treatment Period B, and Follow-up Period 2, blood samples were taken for bone turnover marker evaluation, safety laboratory analysis, markers for disease severity or progression in CRPS (soluble interleukin-2 receptor [sIL-2R]), and (in consenting subjects) for pharmacogenetic and omics testing. Edema of the hand or foot, DMA, PPT, and active range of motion (AROM) were assessed. Patient reported outcomes and quality of life were evaluated using the following questionnaires: Patient Global Impression of Change (PGIC), Patient Global Impression of Severity (PGI-S), EuroQol-5 dimension 5 level (EQ-5D-5L), Patient-Reported Outcomes Measurement Information System (PROMIS®)-29 profile version 2.0 (PROMIS-29 profile) sub-scores: physical function, anxiety, depression, fatigue, sleep disturbance, social roles and activities, and pain interference, Short-Form McGill Pain Questionnaire 2 (SF-MPQ-2), Pain Catastrophizing Scale (PCS), Pain Self Efficacy Questionnaire (PSEQ), and Question EDDEP39 of the PROMIS Item Bank version 1.0 – Emotional Distress – Depression (PROMIS-EDDEP39). The investigator assessed the signs and patient-reported symptoms of CRPS (48-hour recall) for calculation of the CRPS severity score. Vital signs, 12-lead electrocardiograms (ECGs), adverse events, and concomitant medication and therapies were also recorded.

At US sites, medical resources utilization and health economics data were collected on Day 1 and at Week 12, Week 26, Week 36, and Week 52. At the same time points, the subjects at US sites were also asked to complete the Work Productivity and Activity Impairment Questionnaire: CRPS (WPAI: CRPS).

Trial performance

There was 1 protocol amendment, the main aim of which was to include weekly pain intensity assessments after Week 12 using an electronic diary. Full details of the changes are provided in Section 9.8.1.1.

Two similar Phase III pivotal trials were performed to support product registration; this trial and trial KF7013-02.

An interim analysis was planned after a combined total of approximately 80 randomized subjects in the two Phase III trials, KF7013-02 and KF7013-04, had completed Week 12 of treatment and the required data was available in the databases. The planned interim analysis, based on the pooled data of both trials, indicated futility (i.e., it was unlikely that the trials would demonstrate statistical significance of neridronic acid over placebo) and the independent statistician recommended stopping the trials. The Sponsor followed this recommendation and took the decision to stop the trials after the interim analysis.

The handling of subjects already enrolled in the trial when the decision to stop the trials was taken is described in detail in Section 9.8.1.3.

Summary of the statistical methods

The primary analysis was planned to be performed once all subjects had completed Visit 11 (Week 26). Due to the early termination of the trial, the primary analysis was performed on the data that were collected up to the date of last subject out. The planned secondary efficacy analyses and analyses of efficacy related to other data were not performed.

The planned pharmacodynamic and health economic analyses were also not performed.

Sample size rationale

The planned sample size was based on a statistical test of the superiority of 400 mg neridronic acid versus placebo in the primary endpoint. The null hypothesis of no effect, H_0: $0 \leq \mu_{400} - \mu_0$, was tested against the alternative hypothesis H_1: $\mu_{400} - \mu_0 < 0$. (Note: A pain reduction was analyzed as a negative change from baseline. An effective treatment would lead to reduced pain and, hence, to a negative mean change from baseline, $\mu < 0$).

For a difference in the means of $\mu_{400} - \mu_0 = -1.0$ points on the NRS, assuming a standard deviation (SD) of 2.0 points on the NRS and a 1-sided significance level of 2.5% ($\alpha = 0.025$), 86 subjects per arm was required to provide at least 90% power ($1-\beta = 0.9$) to reject the null hypothesis. To compensate for a slight decrease in power due to the optional futility interim analysis, a total of 180 subjects (90 subjects per arm) were planned to be allocated to treatment.

Subject populations

Enrolled Set:	The Enrolled Set included all subjects who signed the informed consent form.
Allocated Set:	The Allocated Set included all subjects who were allocated to treatment.
Safety Set:	All subjects with at least 1 IMP administration, including any partial infusion.
Full Analysis Set (FAS):	All subjects allocated with at least 1 IMP administration, including any partial infusion.

Statistical methods and analysis

The pre-specified analyses for the primary endpoint were performed. The pre-specified analyses for the secondary endpoints were not performed.

The planned analyses for efficacy data evaluated during Treatment Period B and Follow-up Period 2 were not performed.

Safety data before Week 26 were summarized descriptively for subjects initially treated with placebo and subjects initially treated with neridronic acid. Adverse events after Week 26 were summarized descriptively for subjects initially treated with placebo and with no treatment in Treatment Period B, subjects initially treated with placebo and treated with neridronic acid in Treatment Period B, subjects initially treated with neridronic acid and with no treatment in Treatment Period B, and subjects initially treated with neridronic acid and treated with neridronic acid again in Treatment Period B.

Primary endpoint

The primary estimand was the difference in means of the primary efficacy endpoint of 400 mg intravenous neridronic acid compared to placebo for all allocated and treated subjects. This treatment policy or de facto estimand measures the effect of neridronic acid regardless of adherence to treatment or protocol.

The primary estimand was estimated by the analysis of the primary efficacy endpoint for the Full Analysis Set. The primary analysis fitted a mixed-effects model for repeated measures (MMRM) to the change from baseline in the average pain intensity scores from Week 1 to Week 12 recorded once daily in the electronic diary, including the covariate baseline pain intensity score, and the factors geographic region, week, treatment, and treatment-by-week interaction as fixed effects, and an unstructured covariance matrix to model the covariance structure of the repeated measurements.

The primary efficacy analysis was performed using the contrast, i.e., the mixed model Wald test, of neridronic acid 400 mg versus placebo at Week 12 of the treatment, week and treatment-by-week interaction term of the mixed effects model described above. Model-based parameter estimates, standard errors, 95% confidence intervals, and p-values were tabulated. This analysis was performed using only the observed values without imputation of missing values.

Interim analysis

The interim analysis was planned after a combined total of approximately 80 randomized subjects in the two Phase III trials, KF7013-02 and KF7013-04, had completed Week 12 of treatment and the required data was available in the databases. The interim analysis was for futility only and was non-binding. The futility criterion was based on the unblinded comparison of the primary endpoint and was calculated using identical methods as for the final analysis. If the observed difference in the means of μ_{400} - μ_0 was $\geq$ -0.3 points on the NRS, the null hypothesis was not rejected and the recommendation was to stop both trials. The interim analysis was performed by an independent statistician not otherwise involved in the conduct of the trial and the result only stated the recommendation to stop or continue the Phase III program. As the interim analysis was for futility only, no inflation of the type I error would have occurred.

Summary of results

Subject disposition

Overall, 267 subjects were enrolled and 100 of these subjects were allocated to IMP. A total of 99 subjects were treated in Treatment Period A (1 subject was allocated to IMP but was not treated). Ninety subjects completed Treatment Period A and 25 subjects completed Follow-up Period 1. A total of 17 subjects were treated in Treatment Period B and 16 subjects completed Treatment Period B. One subject completed Follow-up Period 2 and completed the trial.

Of the 99 subjects treated with IMP in Treatment Period A, a total of 98 subjects discontinued from the trial: 89 subjects due to other reasons (mainly due to early termination of the trial), 5 subjects due to withdrawal of consent, 2 subjects lost to follow-up, 1 subject due to an adverse event, and 1 subject due to protocol deviations.

Of the 99 subjects treated with IMP in Treatment Period A, 9 subjects did not complete treatment: 8 subjects due to other reasons and 1 subject (in the neridronic acid 400 mg group) due to an

adverse event. Of the 17 subjects treated with IMP in Treatment Period B, 1 subject (who received neridronic acid 400 mg in Treatment Period A) did not complete treatment due to an adverse event.

As the planned interim analysis based on the pooled data from trials KF7013-02 and KF7013-04 indicated futility, the Sponsor took the decision to stop the trials prematurely.

Demographics

For the Safety Set (99 subjects) the mean age was 50.0 years with 88.9% of subjects between 18 and 64 years old and 11.1% between 65 and 84 years old. Overall, 71.7% of the subjects were women. The majority of subjects were White (86.9%) and not Hispanic or Latino (83.8%).

Demographic characteristics were similar among the treatment groups.

Complex regional pain syndrome history

Overall, 71.7% of subjects reported CRPS-I and 14.1% reported CRPS-II. The majority of subjects (90.9%) reported a known precipitating event prior to the onset of symptoms of CRPS. The distribution for the type of precipitating event was as follows: surgery (41.4%), fracture (31.3%), sprain (14.1%), specification of other etiology (14.1%), and crush (5.1%).

The CRPS location was more often on the right side than the left side of the body (54.5% versus 45.5%). The lower extremity was more often affected than the upper extremity for subjects in this trial (64.6% versus 35.4%).

The duration of CRPS, defined as time from onset of symptoms to the Enrollment Visit, ranged from 1.2 months to 23.6 months. The median duration was 12.33 months; the mean duration was 12.48 months.

Efficacy

The interim analysis was performed on a total of 81 subjects; 29 subjects from the KF7013-02 trial and 52 subjects from the KF7013-04 trial. While the interim analysis was performed and until the decision was taken to stop the trials, subjects continued to be enrolled and dosed. As a result, a total of 99 subjects were included in the final analysis of this trial.

The interim analysis, based on the pooled data from trials KF7013-02 and KF7013-04, of the difference between neridronic acid 400 mg and placebo in the mean change from baseline for average pain intensity scores (0.16 on the 11-point NRS) was above the pre-specified futility threshold of -0.3 on the 11-point NRS (note: a pain reduction was analyzed as a negative change from baseline. An effective treatment would lead to reduced pain and, hence, to a negative mean change from baseline). This indication of futility resulted in the trials being stopped early. The outcome of the interim analysis and the early stopping of the trials rendered the outcome of the individual trials inconclusive.

For the analysis performed on the KF7013-04 trial data that were collected up to the date of last subject out, the least squares mean (standard error) for the change from baseline for the average pain intensity scores was -1.71 (0.268) on the 11-point NRS for the placebo group and -1.28 (0.270) on the 11-point NRS for the neridronic acid 400 mg group.

Safety and tolerability

There were no deaths reported during the trial. Seven serious treatment emergent adverse events (TEAEs) were reported in 5 subjects (5.1%): 4 serious TEAEs in 3 subjects (5.9%) in the placebo

group and 3 serious TEAEs in 2 subjects (4.2%) in the neridronic acid 400 mg group. Only 1 of the serious TEAEs was considered by the investigator to be related to IMP (silent myocardial infarction for 1 subject in the neridronic acid 400 mg group). No serious TEAE reported after Visit 11 was classified by the investigator as possibly related to IMP.

Overall, before Visit 11 (Week 26), 260 TEAEs were reported in 80 of 99 subjects (80.8%): 40 subjects (78.4%) reported 130 TEAEs in the placebo group and 40 subjects (83.3%) reported 130 TEAEs in the neridronic acid 400 mg group. Generally, the number of subjects per individual TEAE was low and there was no clear difference in the most frequent TEAEs between the groups; however, nausea tended to be less frequent in the neridronic acid 400 mg group.

After Visit 11, a total of 57 TEAEs were reported in 12 of 99 subjects (12.1%): 1 subject (2.3%) who was not treated during Treatment Period B reported 1 TEAE and 11 subjects (19.6%) who were treated with neridronic acid 400 mg during Treatment Period B reported 56 TEAEs.

Considering the long observation period (up to 52 weeks) and the trial population having many comorbidities, the number of subjects with TEAEs was as expected.

The most common TEAEs before Visit 11 (occurring in more than 7.5% of subjects in any treatment group) are summarized below for the Safety Set.

	Placebo		**Neridronic acid 400 mg**	
	N = 51	**E = 130**	**N = 48**	**E = 130**
Preferred Term	**n (%)**	**e (%)**	**n (%)**	**e (%)**
Acute phase reaction	5 (12.5)	6 (4.6)	8 (20.0)	10 (7.7)
Urine albumin/creatinine ratio increased	1 (2.5)	1 (0.8)	5 (12.5)	5 (3.8)
Influenza like illness	0	-	4 (10.0)	4 (3.1)
Pain in extremity	2 (5.0)	2 (1.5)	4 (10.0)	8 (6.2)
Urinary tract infection	1 (2.5)	1 (0.8)	4 (10.0)	5 (3.8)
Arthralgia	3 (7.5)	3 (2.3)	3 (7.5)	3 (2.3)
Back pain	2 (5.0)	2 (1.5)	3 (7.5)	4 (3.1)
Fatigue	1 (2.5)	1 (0.8)	3 (7.5)	3 (2.3)
Headache	5 (12.5)	8 (6.2)	3 (7.5)	3 (2.3)
Lipase increased	1 (2.5)	1 (0.8)	3 (7.5)	3 (2.3)
Myalgia	0	-	3 (7.5)	3 (2.3)
Pain	1 (2.5)	1 (0.8)	3 (7.5)	3 (2.3)
Vitamin D deficiency	5 (12.5)	5 (3.8)	3 (7.5)	3 (2.3)
Nausea	8 (20.0)	12 (9.2)	2 (5.0)	2 (1.5)
Blood creatine phosphokinase increased	4 (10.0)	5 (3.8)	1 (2.5)	1 (0.8)
Bone pain	3 (7.5)	5 (3.8)	1 (2.5)	1 (0.8)
Complex regional pain syndrome	3 (7.5)	4 (3.1)	1 (2.5)	1 (0.8)
Dizziness	3 (7.5)	3 (2.3)	1 (2.5)	1 (0.8)

% = percentage of subjects with TEAEs or percentage of TEAE, respectively, E = total number of TEAEs, e = number of TEAEs, N = number of subjects, n = number of subjects with TEAE, TEAE = treatment emergent adverse event.

Source: Table 15.3.1.2.1 and Table 15.3.1.3.4

Most of the TEAEs reported before Visit 11 were classified by the investigator as mild or moderate and the numbers of TEAEs in each category were similar in both treatment groups (mild: 69.2% in the placebo group and 71.5% in the neridronic acid 400 mg group; moderate: 23.1% in the placebo group and 26.2% in the neridronic acid 400 mg group. A higher number of severe TEAEs was reported in the placebo group compared to the neridronic acid 400 mg group (7.7% versus 2.3%).

After Visit 11, most of the TEAEs reported overall for neridronic acid were classified by the investigator as moderate (69.6%) or mild (28.6%). Only 1 severe TEAE was reported.

In the neridronic acid 400 mg group, of the TEAEs reported before Visit 11, 60 of 130 TEAEs (46.2%) were considered by the investigator to be related to IMP. In the placebo group, 48 of 130 TEAEs (36.9%) were considered by the investigator to be related to IMP.

Of the TEAEs reported after Visit 11 overall for neridronic acid, 32 of 56 TEAEs (57.1%) were considered by the investigator to be related to IMP.

No subject was permanently discontinued from IMP due to symptomatic hypocalcaemia, deterioration of renal function, QT prolongation, or hypersensitivity to IMP. There were no discontinuations from IMP or from the trial due to pregnancy. There was no indication of a causal relationship with neridronic acid for the discontinuations from IMP or trial.

No clear trends attributable to neridronic acid were observed in laboratory values, vital signs, or ECG data.

Conclusions

Efficacy

- The protocol defined interim analysis on the primary endpoint on pooled data from trials KF7013-02 and KF7013-04 indicated futility and both trials were stopped early before recruitment of the planned sample size was completed. The outcome of the interim analysis and the early stopping of the trials rendered the outcome of the individual trials inconclusive.

Safety

- After intravenous administration of neridronic acid 400 mg in CRPS patients in KF7013-04, the safety and tolerability was in line with the known safety profile of neridronic acid.