SDR-CTR-SYN-06

Trial code	KF7013-03
Title of trial	Open-label safety trial of intravenous neridronic acid in subjects with complex regional pain syndrome (CRPS)
Trial design	Multi-site, open-label, single-arm trial.
Development phase	Phase III
EudraCT number	2016-001164-11 IND number 115811
Universal Trial Number	U1111-1180-8099
Investigational medicinal product	Neridronic acid for intravenous infusion
Indication	Treatment of CRPS
Coordinating investigator	[redacted], MD Universitätsmedizin der Johannes Gutenberg-Universität Mainz Klinik und Poliklinik für Neurologie Langenbeckstrasse 1, 55131 Mainz, Germany
Trial sites	Germany (4 sites), United States (42 sites)
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Sponsor's signatory	Dr [redacted], Clinical Scientist Contact number: +49 (0) 241-569-0
Trial period	First subject in: 20 Dec 2016 Last subject out: 09 Jan 2019

Objectives

Objective	Endpoint/Outcome
Primary	**Primary**
To assess the safety and tolerability of neridronic acid in subjects with CRPS.	• Occurrence of any treatment emergent adverse event (TEAE).
Secondary	**Secondary**
To assess the safety and tolerability of neridronic acid in subjects with CRPS.	• Occurrence of permanent discontinuation from treatment due to an adverse event.
To assess the efficacy of neridronic acid in treatment of CRPS.	• Change from baseline to Week 12 and Week 26 in the current pain intensity score, using a numerical rating scale (NRS). • Response to treatment, defined as at least 30% and at least 50% decrease from baseline in the current pain intensity score, at Week 12 and Week 26. • Patient Global Impression of Change (PGIC) at Week 12 and Week 26. • Change from baseline to Week 12 and Week 26 in the Pain Interference score of the Brief Pain Inventory (BPI).

Investigational medicinal product (IMP)

108 mg sodium neridronate hemi hydrate (equivalent to 100 mg neridronic acid) in a total volume of 8 mL; batch numbers: 09114F (ampules) and P56004A/B (vials); expiration dates: Jul 2017 (ampules) and Aug 2018 (vials).

Trial treatments

The full 8 mL of IMP was diluted in 500 mL normal saline and administered by slow intravenous infusion (240 minutes [maximum 260 minutes]) on Day 1, Day 4, Day 7, and Day 10, resulting in a total dose of 400 mg neridronic acid.

Other medication

Tetracycline hydrochloride 250 mg capsules for oral administration (applicable only for the subset of subjects at US sites undergoing the bone biopsy); batch number: 1116600017; expiration date: Feb 2019.

Trial population

The trial included male or female subjects who were at least 18 years of age with a confirmed diagnosis of CRPS according to the clinical diagnostic criteria recommended by the International Association for the Study of Pain (IASP; "Budapest clinical criteria") at Visit 1. Subjects were required to have ongoing moderate to severe chronic pain, including a baseline current pain intensity score of at least 4 using an 11-point NRS, referring to the CRPS-affected limb, at Visit 2 (prior to dosing).

Subjects had to be on a stable treatment regimen for CRPS for at least 1 month. Subjects must have failed trials of at least 2 treatments for CRPS, one of which had to be a pharmacologic treatment.

Subjects with evidence of renal impairment (estimated glomerular filtration rate [eGFR] less than 60 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine equation), a urinary albumin creatinine ratio (ACR) greater than 150 mg/g, or a history of chronic kidney disease were excluded.

Summary of the trial procedures and assessments

The trial was divided into 3 periods: an enrollment period starting from the Enrollment Visit and lasting for up to 60 days; a 10-day treatment period during which 4 infusions of IMP were administered; and a follow-up period of approximately 50 weeks (from Week 2 to 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 current pain, worst pain, and average pain, the latter 2 ratings using a 24-hour recall.

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, 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 whilst ensuring a minimum period of 48 hours between infusions. During the treatment period and follow-up period, pain intensity ratings (current, worst, and average pain intensity) were captured at the site visits in a patient reported outcome system. Blood samples were taken for bone turnover marker and safety laboratory analysis. Vital signs, 12-lead electrocardiograms (ECGs), adverse events, and concomitant medication and therapies were recorded. Continuous real-time ECG monitoring was performed during infusion visits.

Patient reported outcomes and quality of life were assessed on Day 1, Week 6, Week 12, Week 26, Week 39, and Week 52 using the following questionnaires (completed by the subject using a patient reported outcome system): PGIC, BPI interference scale, Pain Disability Index (PDI), EuroQol-5 dimension 5 level (EQ-5D-5L), Pain Anxiety Symptom Scale (PASS), and Center for Epidemiological Studies Depression Scale (CES-D). The investigator assessed the signs and patient-reported symptoms of CRPS (48-hour recall) on Day 1, Week 6, Week 12, Week 26, Week 39, and Week 52 for calculation of the CRPS severity score.

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

A subset of subjects from sites in the US underwent additional bone densitometry (dual-energy X-ray absorptiometry [DXA] and magnetic resonance imaging (MRI) prior to Day 1 and at Week 26 to evaluate any changes in bone mineral density (BMD) in the lumbar spine and CRPS affected limb relative to the contralateral limb, and the volume of bone marrow lesions in the CRPS affected limb relative to the contralateral limb.

Another subset of subjects from sites in the US underwent a bone biopsy at Week 26 to assess for signs of osteomalacia, based on histology and quantitative bone histomorphometry.

An independent data monitoring committee (DMC) was responsible for periodically reviewing safety information from the trial and monitoring trial conduct and overall progress. The DMC did not request any suspension of the trial or any change to trial conduct requiring a protocol amendment.

Trial performance

There were 4 protocol amendments. There was no premature trial termination or suspension (clinical hold) of the trial.

Summary of the statistical methods

As this was a single-arm trial, no treatment comparisons were conducted, but development from baseline over time was investigated. All analyses in this trial were exploratory. No statistical testing of inference was planned. There was no multiplicity adjustment for any of the analyses. All confidence intervals used to describe the data were determined using a 95% confidence level.

Sample size rationale

The sample size was intended to maximize available safety data in line with the Food and Drug Administration regulatory requirements to support product registration. It was estimated that approximately 290 subjects would be included in this trial.

If the expected number of bone biopsies or bone densitometry and MRI assessments were not obtained, it was not planned to increase the number of subjects included in the trial.

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. The Safety Set was the primary analysis set in this trial.
Full Analysis Set:	All subjects allocated with at least 1 IMP administration, including any partial infusion. In this trial the Full Analysis Set coincided with the Safety Set.
Treatment Completers Set:	All treated subjects who completed IMP administration according to the protocol, i.e., subjects who received the full dose of all 4 planned infusions of IMP.
Pharmacodynamic Set:	All treated subjects with at least 1 non-missing value for at least 1 of the bone turnover markers.
Bone Biopsy Set:	All subjects with at least 1 bone biopsy evaluable for histology or histomorphometry.
Bone Imaging Set:	All subjects with at least 1 DXA or MRI image evaluable for BMD (DXA) or bone marrow lesion volume (MRI).

Statistical methods and analysis

Subject disposition was summarized descriptively for all enrolled subjects and discontinuations were summarized descriptively for all allocated subjects. Demographic data, baseline characteristics, medical history, concomitant medications, and exposure were summarized descriptively for the Safety Set. Pharmacodynamic parameters were summarized descriptively for the Pharmacodynamic Set.

Primary safety endpoint

The primary endpoint of this trial was a binary endpoint assessing whether or not a subject experienced any TEAE. The primary safety endpoint was analyzed in the Safety Set.

Secondary safety endpoints and other safety data

The incidences and incidence rates of all adverse events as well as permanent discontinuations from treatment due to adverse events were summarized descriptively.

The distribution of time to onset of any TEAE was summarized using time-to event methods. A graphical display using Kaplan-Meier methods displaying subjects at risk per time point was produced.

Safety laboratory values (hematology, clinical chemistry, and urinalysis), vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body weight, and body mass index), 12-lead ECG, and further safety parameters were summarized descriptively.

All safety analyses were conducted on the Safety Set.

Efficacy endpoints and other efficacy data

The analysis of all efficacy endpoints and other efficacy data were exploratory and were summarized using descriptive statistics unless stated otherwise. Analyses were performed on all post-baseline measurements.

All efficacy analyses were conducted on the Full Analysis Set.

Handling of missing data

Missing data was not imputed. The number of missing data was included in all descriptive summaries.

Summary of results

Subject disposition

Overall, 580 subjects were enrolled and 318 of these subjects were allocated to IMP. A total of 316 subjects were treated (2 subjects were allocated to IMP but were not treated). A total of 247 subjects completed the trial. Seventy-one subjects discontinued during the course of the trial: 30 subjects due to withdrawal of consent, 26 subjects lost to follow-up, 5 subjects due to other reasons, 4 subjects due to adverse events, 2 subjects due to inclusion/exclusion criteria not met, 1 subject due to lack of efficacy, 1 subject due to death, 1 subject due to protocol deviations, and for 1 subject the reason was missing.

Of the 318 subjects allocated to IMP, 298 subjects completed treatment. Twenty subjects did not complete treatment: 12 subjects due to adverse events, 4 subjects due to other reasons, 3 subjects due to withdrawal of consent, and 1 subject due to death.

Demographics

For the Safety Set (316 subjects) the mean age was 47.4 years and 75.0% of the subjects were women. The majority of subjects were White (94.0%). At the Enrollment Visit, mean body weight was 80.7 kg. Mean body mass index was 28.3 kg/m^2.

Complex regional pain syndrome history

The distribution for the type of precipitating event was as follows: surgery: 139 subjects (44.0%), specification of other etiology: 66 subjects (20.9%), fracture: 64 subjects (20.3%), sprain: 38 subjects (12.0%), and crush: 20 subjects (6.3%).

The CRPS location was evenly distributed between the left (177 subjects [56.0%]) and right side (149 subjects [47.2%]). The lower extremity was more often affected than the upper extremity (217 subjects [68.7%] versus 87 subjects [27.5%]). One hundred and seventeen subjects (37.0%) reported more than 1 limb being affected.

The mean CRPS duration, defined as time from onset of symptoms to the Enrollment Visit, was 6.1 years, the mean time from CRPS precipitating event was 6.1 years, and the mean time from

diagnosis was 4.8 years. Median values were 3.9 years, 4.0 years, and 2.9 years, respectively. The CRPS duration ranged from 0 years to 32 years.

Efficacy

The mean (standard deviation [SD]) baseline current pain intensity, assessed using an 11-point NRS, was similar for the subjects with a CRPS duration ≤2 years (6.33 [1.64]) and for the subjects with a CRPS duration >2 years (6.70 [1.55]).

For the overall population, mean current pain intensity improved until Week 6. After Week 6, only minor changes were observed up until Week 52. At Week 12, the mean (SD) change for the current pain intensity from baseline was -1.54 (2.27). The mean (SD) change from baseline at Week 26 was -1.57 (2.45).

In the subgroup of subjects with a CRPS duration ≤2 years, mean current pain intensity improved beyond Week 6 up until Week 52.

Mean [SD] changes from baseline at both Week 12 and Week 26 were higher for subjects with a CRPS duration ≤2 years compared to subjects with a CRPS duration >2 years (Week 12: -2.15 [2.35] versus -1.27 [2.19]; Week 26: -2.10 [2.65] versus -1.33 [2.32]).

A similar trend was seen for mean average and mean worst pain intensity, also assessed using an 11-point NRS.

In general, a larger reduction in mean pain intensity was observed for subjects with a CRPS duration ≤2 years than for subjects with a CRPS duration >2 years.

At Week 12, more than 30% of subjects were considered to have shown a treatment response (33.2% of subjects reported at least a 30% reduction in current pain intensity and 39.2% of subjects reported at least a 2-point reduction on the NRS scale). The percentages of responders remained stable from Week 6 to Week 52.

At Week 12, 35.7% of subjects rated their overall status as being “much improved” or “very much improved” on the PGIC questionnaire. Subjects with a duration of CRPS ≤2 years reported a better response on the PGIC compared to subjects with a duration of CRPS >2 years.

Better responses were also seen for subjects with a duration of CRPS ≤2 years for the pain interference score of the BPI and the CRPS severity score compared to subjects with a duration of CRPS >2 years.

Pharmacodynamics

Consistent with the known effects of bisphosphonates, there was an early decrease in the bone resorption marker C-terminal telopeptide of type I collagen (CTX) followed by a delayed decrease in the bone formation markers bone alkaline phosphatase (BAP) and procollagen type I amino-terminal propeptide (PINP). Mean levels of all 3 bone turnover markers returned to approximately baseline by Week 52.

Due to the small amount of evaluable imaging data for both MRI and bone densitometry, a meaningful conclusion about the effect of neridronic acid on BMD and bone marrow lesions in the CRPS-affected limb, relative to the contralateral, unaffected limb was difficult to reach. Bone marrow lesions along with other bone abnormalities as well as decreased BMD are anticipated in

CRPS patients based on previously published data. However, bone marrow lesions were detected in only 1 subject at baseline with unchanged volume and severity score at Week 26. An increase was observed in the adjusted total lumbar spine BMD at Week 26 from baseline, however any statistically significant evaluation of BMD should be carefully interpreted due to the high amount of missing data along with the small number of overall cases. On average, there was no relevant difference in BMD between affected and unaffected limbs, and percent changes from baseline to Week 26 in the BMD ratios (affected region of interest [ROI]/unaffected ROI) were small.

Bone biopsy analysis

From the limited data that was evaluable, findings consistent with osteoporosis were reported. There was no excess unmineralized osteoid and no evidence of osteomalacia or other bone tissue abnormalities.

Health economics and work productivity evaluation

The proportion of subjects who were employed remained stable throughout the trial.

From Day 1 to Week 26, the proportion of subjects who did not miss any hours from work increased and then remained stable until Week 52.

From Day 1 to Week 26, there appeared to be a reduction in how much CRPS affected the subjects' productivity while working (as rated on a 0 to 10 scale). This reduction was maintained until Week 52.

At Week 52, there appeared to be a slight improvement in how much CRPS affected the subjects' ability to do their regular daily activities (other than work) as rated on a 0 to 10 scale.

Between Day 1 and Week 26, there was a reduction in the number of subjects who had used their primary care provider or pain specialist within the last 26 weeks. This reduction was maintained until Week 52.

Safety and tolerability

The number of subjects with related serious adverse events and with TEAEs leading to discontinuation was low. One death (due to pneumonia) occurred during the trial. This was not considered to be related to the IMP by the investigator. Overall, 30 serious TEAEs were reported in 27 subjects (8.5%). Three serious TEAEs reported for 3 subjects (1 serious TEAE each) were considered by the investigator to be at least possibly related to the administration of IMP: chest pain and myalgia (both of which resulted in hospitalization), and liver disorder (which was considered medically significant). Twenty TEAEs in 12 subjects (3.8%) led to discontinuation from IMP. Seven TEAEs led to discontinuation from the trial for 6 subjects (1.9%).

One or more TEAE was reported by 277 subjects (87.7%). However considering the long observation period (up to 52 weeks), the trial population having many comorbidities, and the majority of TEAEs (55.9%) not being considered related, the number of subjects with TEAEs is as expected.

The most common TEAEs (occurring in more than 5% of subjects) are summarized below for the Safety Set.

SDR-CTR-SYN-06

Primary System Organ Class Preferred Term	Neridronic acid 400 mg N = 316 n (%)	 E = 1369 e (%)
All System Organ Classes	277 (87.7)	1369 (100)
Gastrointestinal disorders	80 (25.3)	128 (9.3)
Nausea	34 (10.8)	46 (3.4)
General disorders and administration site conditions	127 (40.2)	232 (16.9)
Condition aggravated	31 (9.8)	45 (3.3)
Fatigue	32 (10.1)	39 (2.8)
Pain	28 (8.9)	37 (2.7)
Pyrexia	18 (5.7)	19 (1.4)
Musculoskeletal and connective tissue disorders	132 (41.8)	285 (20.8)
Arthralgia	27 (8.5)	31 (2.3)
Back pain	25 (7.9)	30 (2.2)
Bone pain	17 (5.4)	20 (1.5)
Myalgia	53 (16.8)	71 (5.2)
Pain in extremity	25 (7.9)	30 (2.2)
Nervous system disorders	106 (33.5)	168 (12.3)
Headache	65 (20.6)	96 (7.0)

Adverse events are coded according to MedDRA version 21.1.

E = total number of TEAEs; e = number of TEAEs; MedDRA = Medical Dictionary for Regulatory Activities; N = total numbers of subjects; n = number of subjects;.

Source: [redacted]

Most of the 1369 TEAEs reported were classified by the investigator as mild (810 TEAEs [59.2%]). The number of severe TEAEs reported during the trial was low (73 TEAEs [5.3%]).

Overall, 604 TEAEs (44.1%) were considered by the investigator to be at least possibly related to the administration of IMP.

A total of 66 subjects reported 98 TEAEs associated with the acute phase reaction (including headache, myalgia, pain, fatigue, pyrexia, influenza like illness, arthralgia, bone pain, chills, musculoskeletal chest pain, musculoskeletal pain, and pain in extremity, but only if occurring in the first 3 days after first IMP intake and not lasting longer than 3 days).

No subject was permanently discontinued from IMP due to symptomatic hypocalcemia, deterioration of renal function, QT prolongation, or hypersensitivity to IMP. There were no discontinuations from IMP or from the trial due to pregnancy. No suggestive pattern was observed for the discontinuations from IMP due to liver-related disorders. There was no indication of a causal relationship with neridronic acid for the discontinuations from IMP or trial.

Mean serum calcium values decreased during treatment and returned to baseline as expected. Mean parathyroid hormone values increased during treatment and decreased back to normal over the course of the trial. In addition, mean BAP values decreased as expected and increased back to normal over the course of the trial. These observations support ongoing mineralization with neridronic acid.

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

Conclusions

Safety

- After intravenous administration of neridronic acid 400 mg in CRPS patients, the tolerability was in line with the known safety profile of neridronic acid.
- The pattern of adverse events observed was similar to that already known for neridronic acid.

Efficacy

- The efficacy results should be interpreted with caution considering the open-label design of the trial with no comparator arm.
- In the total population, pain improved until Week 6; afterwards only minor changes were observed until Week 52.
- For subjects with a CRPS duration ≤2 years, pain improved beyond Week 6 until Week 52.
- Subjects with a CRPS duration ≤2 years showed better pain reduction than subjects with a CRPS duration >2 years.
- More than 30% of subjects experienced a response defined as either at least 30% pain reduction or at least 2 points reduction on the 11-point NRS scale.
- The percentages of responders remained stable from Week 6 to Week 52.
- On the PGIC questionnaire, more than 30% of subjects rated their overall status at any time point as “much improved” or “very much improved”.