



SDR-PRO-TEMPLATE-02

Trial code:	KF7013-02
Title of trial:	Randomized, double-blind, placebo-controlled trial investigating the efficacy and safety of intravenous neridronic acid in subjects with complex regional pain syndrome (CRPS)
Brief title:	Efficacy and safety of intravenous neridronic acid in CRPS
Indication:	Treatment of CRPS
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Trial sites:	Multi-site trial (approximately 80 sites in the United States, European Union, and other regions). Documentation of the involved trial sites will be maintained.
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a) Contact detail changes during the course of the trial will be documented and do not require a protocol amendment.

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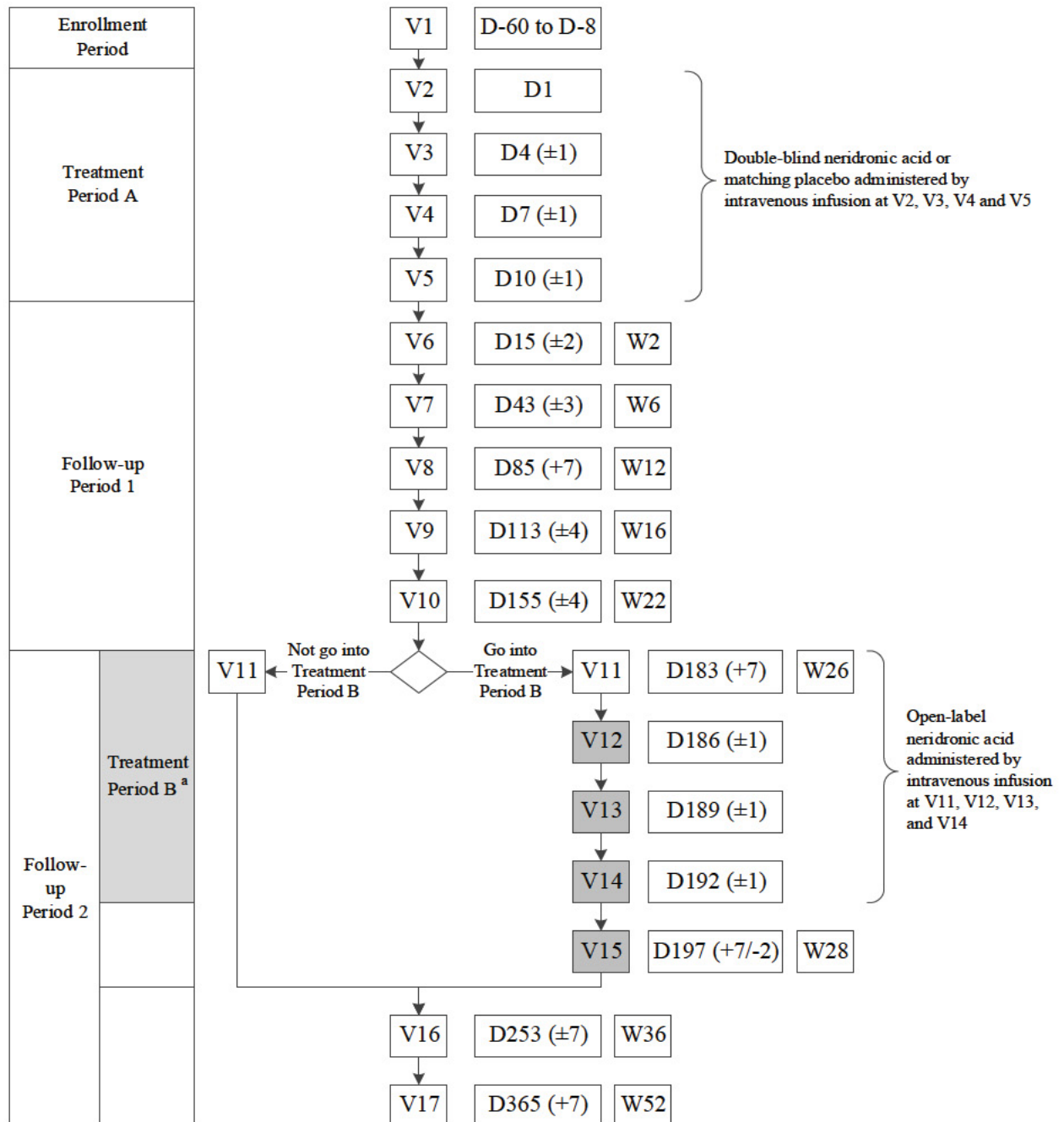
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1 PROTOCOL SYNOPSIS

1.1 Trial design

This is a multi-site, randomized, double-blind, placebo-controlled, 2-arm, Phase III trial of intravenous neridronic acid in subjects with CRPS.

1.1.1 Flow diagram summary of the trial



If Visit 11 is not performed on Day 183, Visit 12 to Visit 15 should proceed in accordance with the originally scheduled time windows relative to Visit 11.

a) Subjects going into Treatment Period B only.

D = Day, V = Visit, W = Week.

1.1.2 Brief description of the sequence and duration of all trial periods

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

At Visit 11 (Week 26), subjects not meeting the pre-specified criteria to continue into Treatment Period B (see Section 1.3.3) will continue in Follow-up Period 2 until Visit 17 (Week 52). Subjects meeting the pre-specified criteria will enter the open-label Treatment Period B with 4 additional infusions over 10 days and follow-up visits until Visit 17 (Week 52).

Each subject is expected to be in the trial for approximately 14 months.

See Section 1.1.1 for a summary of the trial as a flow diagram and Section 1.7 for tabular schedules of events.

1.2 Trial objectives, endpoints, and outcomes

Objective	Endpoint/Outcome	Measure description and timeframe
Primary	Primary	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.	Change from baseline to Week 12 in the average pain intensity score (weekly average of pain values recorded daily in the electronic diary).	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.
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.

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 on the dynamic mechanical allodynia (DMA).	Change from baseline to Week 12 in the pain intensity level of DMA.	<p>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.</p> <p>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.</p> <p>The change from baseline (Visit 2 [Day 1]) to Visit 8 (Week 12) will be analyzed.</p>
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.	<p>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).</p> <p>The ratio of the thresholds of the affected limb versus the unaffected limb will be calculated.</p> <p>The change from baseline (Visit 2 [Day 1]) to Visit 8 (Week 12) will be analyzed.</p>
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.	<p>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.</p> <p>The ratio of the averages of the affected limb versus the unaffected limb will be calculated.</p> <p>The change from baseline (Visit 2 [Day 1]) to Visit 8 (Week 12) will be analyzed.</p>

Other data to be collected that are not directly attributed to or considered as an endpoint

General note: All efficacy and safety data evaluated during Treatment Period B and Follow-up Period 2 will be analyzed descriptively separately for subjects who are treated in Treatment Period B and subjects who are not treated. For subjects treated in Treatment Period B, analyses will be performed for subjects initially treated with placebo and subjects initially treated with neridronic acid.

All efficacy assessments will be evaluated for the time points indicated in the schedules of events.

To assess the efficacy of neridronic acid in subjects with CRPS

- Change from baseline in average pain intensity recorded on the tablet computer.
 - Change from Week 26 in average pain intensity recorded on the tablet computer.
 - Pain response to treatment, defined as at least 50% decrease from baseline in the average pain intensity, based on pain intensity recordings on the tablet computer.
 - Pain response to treatment, defined as at least 50% decrease from Week 26 in the average pain intensity, based on pain intensity recordings on the tablet computer.
 - Pain response to treatment, defined as at least 30% decrease from baseline in the average pain intensity, based on pain intensity recordings on the tablet computer.
 - Pain response to treatment, defined as at least 30% decrease from Week 26 in the average pain intensity, based on pain intensity recordings on the tablet computer.
 - Change from baseline in pain intensity scores determined using worst and current pain ratings recorded daily in the electronic diary.
 - Change from baseline in worst and current pain intensity ratings, recorded on the tablet computer.
 - Change from Week 26 in worst and current pain intensity ratings, recorded on the tablet computer.
 - Duration of effect based on average pain intensity recordings in the electronic diary.
 - Change from baseline in the pain intensity level of DMA.
 - Change from baseline in PPT ratios.
 - Change from baseline in the ratio of the figure of eight measurements of the affected limb versus the unaffected limb.
 - Change from baseline in the active range of motion (AROM) ratio (affected limb and unaffected limb) measured in the hand or foot, respectively.
 - Change from baseline in the CRPS Severity Score.
 - Patient Global Impression of Change (PGIC).
 - Patient Global Impression of Severity (PGI-S).
 - Change from baseline in the EuroQoL-5 Dimension-5 level (EQ-5D-5L) index score and the health-related visual analog scale (VAS) score.
 - Change from Week 26 in the EQ-5D-5L index score and the health-related VAS score.
 - Change from baseline in the responses to questions on the following questionnaires (recorded on the tablet computer):
 - 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). The change from baseline to Week 16 and Week 22 will be assessed for question number 29, GLOBAL07 only.
 - The 6 neuropathic pain items of the Short-Form McGill Pain Questionnaire 2 (SF-MPQ-2) (single items and the combined score).
 - Pain Catastrophizing Scale (PCS).
 - Pain Self Efficacy Questionnaire (PSEQ).
 - Response to Question EDDEP39 of the PROMIS Item Bank version 1.0 – Emotional Distress – Depression (PROMIS-EDDEP39) (recorded on the tablet computer).
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- Concomitant analgesic medication use.
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To describe the trial population and to evaluate subject eligibility

- Demographic data, medical history, dental history, CRPS history, prior medication and therapies, beta-human chorionic gonadotropin (β -HCG) pregnancy test, and drugs of abuse test.
-

To assess the safety and tolerability of neridronic acid in subjects with CRPS

- Adverse events, concomitant medications, physical examination findings, 12-lead electrocardiograms (ECGs), vital signs, body weight, and safety laboratory data.
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To assess the pharmacodynamics of neridronic acid in subjects with CRPS

- Concentrations of bone turnover markers in serum: (C-terminal telopeptide of type I collagen [CTX], bone alkaline phosphatase [BAP], and procollagen type I amino-terminal propeptide [PINP]).
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To assess the pharmacokinetics of neridronic acid in subjects with CRPS

- Concentrations of neridronic acid in plasma.
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To assess health economics and work productivity (US sites only)

- Work Productivity and Activity Impairment Questionnaire: CRPS (WPAI: CRPS).
 - Medical resources utilization.
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To explore markers for disease severity or progression in CRPS

- Concentrations of soluble interleukin-2 receptor (sIL-2R).
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1.3 Trial subjects – the population to be studied

1.3.1 Inclusion criteria

Subjects are eligible for the trial if all the inclusion criteria apply. Subjects will only receive investigational medicinal product (IMP) if documentation is available showing that they meet all of these inclusion criteria.

1. Informed consent signed.
2. Male or female subjects at least 18 years of age at Visit 1.
3. A diagnosis of CRPS according to the clinical diagnostic criteria recommended by the International Association for the Study of Pain (IASP; “Budapest clinical criteria”), assessed at Visit 1. Signs and symptoms of CRPS must apply to an affected limb (arm or leg) and must demonstrate asymmetry with respect to the contralateral limb. The CRPS duration must be 2 years or less since onset of symptoms.
4. 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). The baseline average pain intensity score will be calculated automatically by the electronic diary, which must be checked prior to allocation at Visit 2. A subject who has not met average baseline pain intensity requirements (at least 4 average pain intensity ratings) due to lack of compliance with the electronic diary may be rescheduled for Visit 2 (1 time only), with appropriate re-training to ensure compliance with use of the electronic diary.
5. In stable treatment and follow-up therapy for CRPS for at least 1 month prior to allocation to treatment (Visit 2). Subjects must have failed attempts with at least 2 available treatments for CRPS, 1 of which must have been a pharmacologic treatment.

6. Women of child-bearing potential must have a negative urine β -HCG pregnancy test at Visit 1 and must be using 2 forms of medically acceptable contraception, including at least 1 highly effective method of contraception with a low failure rate, defined as less than 1% per year (e.g., oral contraceptives or intrauterine device), and a second medically acceptable method such as use of condoms with spermicide by their male partner. A barrier method alone is not acceptable. Highly effective methods of contraception must be used for at least 1 month prior to Visit 2 and for the duration of the trial.
7. Subjects must be able to communicate meaningfully, be able to differentiate with regard to location and intensity of the pain, and be able to answer the questions in the questionnaires used in this trial (assistance in filling out the questionnaires may be provided, if required due to motor or other physical impairment).

1.3.2 Exclusion criteria

Subjects will not be eligible for the trial if any of the following exclusion criteria apply. Subjects will only receive IMP if documentation is available showing that they do not meet any of these exclusion criteria.

1. Evidence of severe renal impairment (estimated glomerular filtration rate [eGFR] less than 30 mL/min/1.73 m² using the 2009 Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine equation [Levey et al. 2009] or a urinary albumin to creatinine ratio [ACR] greater than 150 mg/g), based on central safety laboratory data obtained prior to Visit 2. Note: a single repeat laboratory test is allowed.
2. Serum calcium or magnesium outside of the central laboratory's reference range, based on central safety laboratory data obtained prior to Visit 2 (2 repeat laboratory tests are allowed); a history of hypocalcemia or a metabolic disorder anticipated to increase risk for hypocalcemia (e.g., hypoparathyroidism); anticipated need for any new drug with known potential to cause hypocalcemia (e.g., aminoglycosides, new treatment with or dose adjustment of loop diuretics) during the trial.
Subjects on a stable dose of loop diuretics may receive treatment with IMP as long as no dosage increases in the diuretic medication are anticipated and calcium levels are in the reference range.
3. Vitamin D deficiency, defined as a 25(OH)D level less than 30 ng/mL (75 nmol/L), based on central safety laboratory data obtained prior to Visit 2 (up to 4 repeat laboratory tests are allowed). Subjects with vitamin D deficiency should receive appropriate supplementation during the Enrollment Period. A vitamin D level of at least 30 ng/mL (75 nmol/L) must be documented prior to allocation to IMP.
4. Corrected QT interval (according to Fridericia's formula; QTcF) greater than 470 ms (average of 3 ECGs obtained at Visit 1) according to central ECG reading facility evaluation or QTcF greater than 470 ms at pre-dose ECG at Visit 2 according to the investigator's judgment; serum potassium outside the central laboratory's reference range at Visit 1 (a single repeat laboratory test is allowed); clinically unstable cardiac disease, including: unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or an indwelling pacemaker; evidence of complete left bundle branch block; complete atrioventricular block; history of Long QT Syndrome or a relative with this condition; or any history of or other known risk factor for torsade de pointes.

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5. Subjects receiving medications with a known risk of torsades de pointes within 7 days prior to allocation. Subjects receiving selective serotonin re-uptake inhibitor antidepressants (e.g., citalopram, escitalopram) are eligible if the QT interval values do not meet the exclusion criteria, the medication was started at least 1 month prior to Visit 1, the dose is stable, and the dose is anticipated to remain stable throughout the trial.
 6. Any prior use of a bisphosphonate for treatment of CRPS, any prior administration of a bisphosphonate within the previous year, anticipated requirement for treatment with a bisphosphonate for another condition such as osteoporosis during the trial, or administration of denosumab (Prolia[®]) or other bone turnover suppressing drugs within 6 months prior to Visit 1.
 7. History of any allergic or hypersensitivity reaction to neridronic acid or other bisphosphonate, acetaminophen, or to vitamin D or calcium supplements.
 8. Recent tooth extraction or other invasive dental procedure (within 3 months prior to Visit 1), unhealed or infected extraction site, or significant dental/periodontal disease (e.g., impacted molars, severe tooth decay, foci of infection) that may pre-dispose to need for tooth extraction or other invasive dental procedures during the trial. Subjects with indeterminate, suspicious or unreliable dental history, in the opinion of the investigator, must undergo a dental examination prior to receiving treatment.
 9. Evidence of denture-related gum trauma or improperly fitting dentures causing injury.
 10. Prior radiation therapy of the head or neck (within 1 year of Visit 1).
 11. History of malignancy within 2 years prior to Visit 1, with the exception of basal cell carcinoma.
 12. Use of nerve blocks, ketamine infusions, intravenous immunoglobulin, acupuncture, electromagnetic field treatment, or initiation/implementation of radiofrequency ablation or other sympathectomy procedures, or peripheral nerve stimulation within 6 weeks prior to Visit 1.
 13. Evidence of current alcohol or drug abuse, or history of alcohol or drug abuse within 2 years of Visit 1, based on subject history and physical examination and according to the investigator's judgment.
 14. Any other severe medical condition, including severe depression, or any other severe mood disorder, that in the opinion of the investigator may affect efficacy or safety assessments or may compromise the subject's safety during trial participation.
 15. Women who are pregnant or breastfeeding.
 16. Elevated aspartate aminotransferase or alanine aminotransferase greater than 2-fold upper limit of normal, based on central safety laboratory data obtained at Visit 1, or current evidence of chronic liver disease. Safety laboratory testing may be repeated prior to Visit 2, and subjects will be allowed in the trial if results of 2 consecutive tests, at least 3 days apart, are less than or equal to 2-fold upper limit of normal.
 17. Participation in another investigational drug trial within 3 months prior to Visit 1, or any previous trial involving neridronic acid.
 18. Subject is engaged in litigation related to their disability from CRPS in which monetary gain or loss (or other compensation) may affect their objective participation in the trial.
 19. Subjects taking forbidden concomitant medications/therapies or not being able to follow the rules of use of concomitant treatment (see Section 1.4.2).

20. Subjects incapable of giving informed consent.

1.3.3 Criteria to continue into Treatment Period B

Safety laboratory tests will be taken at Visit 10. In case the serum calcium and/or vitamin D levels meet the exclusion criteria to continue into Treatment Period B, additional supplementation similar to the Enrollment Period is allowed between Visit 10 and Visit 11. In case of any safety laboratory retesting, the scheduling and time window of Visit 11 must not be affected.

The decision regarding whether a subject will continue into Treatment Period B will be taken at Visit 11, based on the following criteria:

- A value of at least 4 on the pain intensity question (question number 29, GLOBAL07) of the PROMIS-29 profile at Visit 11.
- The following exclusion criteria are not met:
 - Evidence of severe renal impairment (eGFR less than 30 mL/min/1.73 m² using the 2009 CKD-EPI creatinine equation [Levey et al. 2009] or a urinary ACR greater than 150 mg/g), based on central safety laboratory data obtained prior to Visit 11. A single repeat laboratory test is allowed.
 - Corrected QT interval (QTcF) greater than 470 ms (average of 3 ECGs obtained at Visit 10) according to the central ECG reading facility evaluation or QTcF greater than 470 ms at pre-dose ECG at Visit 11 according to the investigator's judgment; serum potassium outside the central laboratory's reference range at Visit 10 (a single repeat laboratory test is allowed); clinically unstable cardiac disease, including: unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or an indwelling pacemaker; evidence of complete left bundle branch block; complete atrioventricular block; any other known risk factor for torsade de pointes.
 - Subjects receiving medications with a known risk of torsades de pointes within 7 days prior to re-allocation.
 - Subjects taking forbidden concomitant medications/therapies or not being able to follow the rules of use of concomitant treatment (see Section 1.4.2).
 - Recent tooth extraction or other invasive dental procedure (within 3 months prior to Visit 11), unhealed or infected extraction site, or significant dental/periodontal disease (e.g., impacted molars, severe tooth decay, foci of infection) that may pre-dispose to need for tooth extraction or other invasive dental procedures during the further course of the trial.
 - Serum calcium or magnesium outside of the central laboratory's reference range, despite appropriate supplementation between Visit 10 and Visit 11, based on the last central safety laboratory data obtained prior to Visit 11. One repeat laboratory test is allowed.
 - Vitamin D deficiency prior to IMP re-allocation, defined as a 25(OH)D level less than 30 ng/mL (75 nmol/L), based on the last central safety laboratory data obtained prior to Visit 11, i.e., inability to normalize 25(OH)D levels to at least 30 ng/mL (75 nmol/L) despite appropriate supplementation between Visit 10 and Visit 11. Two repeat laboratory tests are allowed (with a minimum interval of 3 days).

- Elevated aspartate aminotransferase or alanine aminotransferase greater than 2-fold upper limit of normal, based on central safety laboratory data obtained at Visit 10, or current evidence of chronic liver disease. A single repeat laboratory test is allowed.
- No other criterion for trial and/or IMP discontinuation is met.

The subjects and investigators will stay blinded to the treatment that the subject received in Treatment Period A.

If, at Visit 11, the criteria to continue into Treatment Period B are not met, the subjects will not receive any further IMP infusion and will continue with the follow-up visits Visit 16 and Visit 17. Subjects can only start Treatment Period B at Visit 11.

1.4 Trial treatments

1.4.1 Investigational medicinal products

The IMPs used in this trial are neridronic acid and matching placebo.

Investigational medicinal product is supplied in glass vials, each containing 108 mg sodium neridronate hemi hydrate (equivalent to 100 mg neridronic acid) or matching placebo in a total volume of 8 mL.

For subjects with no or mild renal impairment, the full contents of a single vial (8 mL) will be diluted in 500 mL normal saline and administered by slow intravenous infusion (240 minutes [maximum 260 minutes]) 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, the full contents of a single vial (8 mL) will be diluted in 500 mL normal saline and administered by slow intravenous infusion (240 minutes [maximum 260 minutes]) at Visit 11, Visit 12, Visit 13, and Visit 14, resulting in a total dose of 400 mg neridronic acid.

All infusions must be performed at the trial site under the supervision of medical staff.

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

CKD-EPI Stage 3a (eGFR 45 mL/min/1.73 m² to <60 mL/min/1.73 m²)

6 mL of solution from a single vial (corresponding to neridronic acid 75 mg) will be 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 m² to <45 mL/min/1.73 m²)

5 mL of solution from a single vial (corresponding to neridronic acid 62.5 mg) will be 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.

For additional requirements related to the IMP infusion, please refer to Section 10.2 of the trial protocol.

1.4.2 Prior/concomitant medications or therapies

Subjects participating in the trial must be on stable therapy prescribed for CRPS, including any multidisciplinary treatment program (e.g., consisting of physical therapy, occupational therapy, cognitive behavioral therapy, and/or graded motor imagery, including mirror feedback). Initiation of a new interdisciplinary treatment program during the trial is prohibited. Other allowed therapies, such as spinal cord stimulation, may be continued during the trial if they are stable for at least 1 month prior to the start of treatment.

Subjects may continue treatment with allowed concomitant medications, including any stable analgesic regimens consisting of opioids and other analgesics, if they are on a stable, well-defined treatment regimen for at least 1 month before allocation to IMP and are anticipated to be able to maintain the treatment regimen up to and including Visit 8 at a minimum in the opinion of the investigator. A prescribed regimen including an as needed dosing schedule is permitted. A subject who does not take prescription analgesics but does take over-the-counter analgesics is permitted to participate if considered stable and anticipated to be able to continue taking only over-the-counter and non-prescription analgesics up to and including Visit 8 at a minimum. Over-the-counter analgesics must remain stable throughout the trial, up to and including Visit 8 at a minimum. After Visit 10, investigators should assess the further need of concomitant treatment for CRPS, in particular opioids, and evaluate if the dose or frequency of these treatments can be decreased, or if treatment can be stopped completely. Any resulting changes must be documented in the electronic case report form (eCRF). Subjects receiving treatment in Treatment Period B should remain on stable analgesic treatment (including over-the counter analgesics) between Visit 11 and Visit 16.

In the event a subject experiences a severe pain flare related to CRPS, trauma, or other reason, a course of short-acting analgesics, including opioids, may be prescribed for up to 2 weeks. The concomitant medication must be documented in the eCRF and the sponsor or sponsor's representative (i.e., medical monitor) must be notified.

To alleviate the expected flu-like symptoms (acute phase reaction) potentially associated with the first intravenous administration of bisphosphonates, all subjects in both treatment groups must receive oral acetaminophen (paracetamol) starting from approximately 1 hour prior to the first infusion of IMP and then approximately every 6 hours for the 72-hour period after the first infusion in Treatment Period A and Treatment Period B. Commercially available doses of acetaminophen (paracetamol) can be used as available in the country where the trial is performed. However, the total dose of acetaminophen, including any other medications that contain acetaminophen, must not exceed the maximum allowed dose according to the local product information, and not more than 4 g/day, due to acetaminophen's known risks for hepatic toxicity. Non-steroidal anti-inflammatory drugs should not be used to alleviate the symptoms of the acute phase reaction due to their potential to cause acute changes in renal function, which may confound renal safety assessments.

All subjects will be provided with supplemental calcium and vitamin D, starting from Visit 1 and continuing through to the end of the trial. Calcium and vitamin D supplementation are considered standard of care for patients treated with bisphosphonates and other drugs that inhibit bone turnover. An appropriate daily supplement should be provided to subjects (recommended doses are 500 mg/day to 1000 mg/day calcium and approximately 1000 IU/day vitamin D as locally authorized); if a subject is currently taking calcium and vitamin D supplements, these may be continued without need for additional supplementation, provided levels of supplementation are

similar to those recommended above. A combination product of calcium and vitamin D may be used. Subjects with vitamin D below 30 ng/mL (75 nmol/L) should receive higher doses of vitamin D during the Enrollment Period (e.g., 10 000 IU/day for 10 days), to meet the protocol-required vitamin D levels prior to starting treatment at Visit 2 and prior to starting treatment at Visit 11. As repletion of vitamin D to these levels can be difficult, repeated laboratory testing for vitamin D is permitted during the Enrollment Period (up to a maximum of 4 times in 60 days) and between Visit 10 and Visit 11 (up to a maximum of 2 times). High doses of vitamin D should not be continued after the subject reaches vitamin D targets (supplementation should continue at the recommended daily dose of approximately 1000 IU/day).

With regard to the calcium and vitamin D supplements, the investigator should promote compliance by instructing the subject to take the supplements as prescribed and by stating that compliance is necessary for the subject's safety. Subjects should be instructed to contact the investigator if they are unable for any reason to take the supplements as prescribed. When used as daily supplements in this trial, calcium and vitamin D are not to be considered as an IMP or a medical treatment for an adverse event.

1.4.2.1 Forbidden concomitant medications

The following medications are forbidden for the duration of the trial or as specified:

- Any experimental or investigational treatment or therapy.
- High-dose opioid analgesics (greater than 200 mg oral morphine equivalent daily dose) or combinations of opioids and benzodiazepines or any other treatment regimens that may have potential for significant opioid/sedatives side effects and that may be considered unstable or unsafe (according to the judgment of the investigator).
- Concomitant use of drugs with the potential to cause hypocalcemia (e.g., aminoglycosides). Subjects on a stable dose of loop diuretics may be allocated to IMP as long as no dosage increases in the diuretic medication are anticipated and calcium levels are in the reference range.
- Oral, intravenous, or intramuscular bisphosphonates, calcitonin, denosumab, anti-angiogenic drugs or other bone-active drugs (e.g., teriparatide).
- Drugs with risk for torsades de pointes as specified:
 - Drugs with a known risk of torsades de pointes within 7 days prior to allocation and throughout the trial.
 - With the following exceptions: selective serotonin re-uptake inhibitor antidepressants (e.g., citalopram, escitalopram), if QT interval values met entry criteria, subjects were on a stable dose for at least 1 month prior to Visit 1, and doses are expected to stay stable throughout the trial.
- Concomitant administration of non-steroidal anti-inflammatory drugs or any other agents with the potential to interfere with the assessment of potential changes in renal function (e.g., angiotensin converting enzyme inhibitors) until 2 weeks after the last IMP administration per treatment period, unless subjects are receiving a stable dose for at least 1 month prior to Visit 1. Non-steroidal anti-inflammatory drugs should not be used to alleviate the symptoms of the acute phase reaction.

- Use of nerve blocks, ketamine infusions, intravenous immunoglobulin, acupuncture, electromagnetic field treatment, initiation/implementation of radiofrequency ablation or other sympathectomy procedures, or peripheral nerve stimulation, within 6 weeks prior to Visit 1 and for the entire duration of the trial.
- Use of systemic steroids starting 2 weeks prior to Visit 1 and for the entire duration of the trial.

1.5 Statistical analyses

The primary analysis will be performed once all subjects have completed Visit 11 (Week 26), including database lock and unblinding. The results from this 26-week analysis will be reported in an interim integrated clinical trial report.

The final analysis of this trial, including Treatment Period B and Follow-up Period 2, will be performed after the last subject has completed the trial and the database has been locked.

1.5.1 Sample size rationale

The sample size is 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, $H_0: 0 \leq \mu_{400} - \mu_0$, is tested against the alternative hypothesis $H_1: \mu_{400} - \mu_0 < 0$. (Note: A pain reduction will be analyzed as a negative change from baseline. An effective treatment will 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 of 2.0 points on the NRS and a 1-sided significance level of 2.5% ($\alpha = 0.025$), 86 subjects per arm will be 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 an optional futility interim analysis, a total of 180 subjects (90 subjects per arm) are planned to be allocated to treatment.

1.5.2 Subject populations

Enrolled Set:	The Enrolled Set includes all subjects who signed the informed consent form.
Allocated Set:	The Allocated Set includes all subjects who are allocated to treatment.
Safety Set:	All subjects with at least 1 IMP administration, including any partial infusion.
Full Analysis Set:	All subjects allocated with at least 1 IMP administration, including any partial infusion.
Pharmacokinetic Set:	All subjects with at least 1 evaluable pharmacokinetic concentration.
Pharmacodynamic Set:	All treated subjects with at least 1 non-missing value for at least 1 of the bone turnover markers.

1.5.3 Statistical methods and analysis

The analysis of primary and secondary efficacy endpoints is described in the subsections below. All other efficacy endpoints will be descriptively summarized in the Full Analysis Set. Confirmatory

testing will be performed for the primary endpoint and for selected secondary endpoints. Further analyses may be done, including statistical hypothesis tests, but all analyses will be exploratory in nature and will not provide confirmatory evidence.

Subject disposition as well as demographic and baseline data and other subject characteristics, e.g., medical history and prior and concomitant medications, will be descriptively summarized for the Full Analysis Set and the Safety Set.

Adverse events, laboratory values, ECG, vital signs, and further safety parameters will be summarized descriptively for the Safety Set. All laboratory parameters will be collected both in SI units and US conventional units. All parameters will be reported in SI units and, in addition, selected laboratory parameters will be reported also in US conventional units (dual reporting).

Pharmacokinetic concentrations will be analyzed in the Pharmacokinetic Set. Descriptive statistics of the observed neridronic acid plasma concentrations at the planned time windows will be created. Owing to the sparse sampling and the random time points, no derivation and analysis of non-compartmental pharmacokinetic parameters is foreseen.

Bone turnover marker values will be descriptively summarized by parameter for the Pharmacodynamic Set.

Health economics and work productivity data will be summarized descriptively for the Full Analysis Set.

Analysis of sIL-2R concentrations will be summarized descriptively for the Safety Set.

All efficacy and safety data evaluated during Treatment Period B and Follow-up Period 2 will be analyzed descriptively separately for subjects who are treated in Treatment Period B and subjects who are not treated. For subjects treated in Treatment Period B, analyses will be performed for subjects initially treated with placebo and subjects initially treated with neridronic acid.

1.5.3.1 Primary endpoint

See Section 1.2 for the definition of the primary endpoint.

For the primary objective of the trial, the primary estimand is 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 will be estimated by the analysis of the primary efficacy endpoint for the Full Analysis Set. The primary analysis will fit a mixed 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 will be 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 will be tabulated. This analysis will be performed using only the observed values without imputation of missing values.

Additional sensitivity analyses will be performed to assess the robustness of primary analysis results. Sensitivity analyses will include the imputation of missing pain intensity scores using different pattern mixture models (PMMs).

A descriptive summary of the weekly averages and the changes from baseline will be generated by treatment group. Graphical displays will be used if appropriate.

1.5.3.2 Secondary efficacy endpoints

All secondary efficacy endpoints will be analyzed for the Full Analysis Set.

Average pain intensity

The change from baseline in the average pain intensity, recorded on the tablet computer, will be analyzed with an MMRM, including the covariate baseline pain intensity score, and the factors geographic region, week, treatment, and treatment-by-week interaction as fixed effects, and subject as random effect. An unstructured covariance matrix will be used to model the covariance structure.

The analysis will be performed using the contrast, i.e., the mixed model Wald test, of 400 mg neridronic acid versus placebo at Week 26 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 will be tabulated. This analysis will be performed using the observed values without imputation of missing values.

Pain response to treatment

Pain response to treatment, defined as an at least 30% decrease from baseline in average pain intensity, recorded on the tablet computer, will be derived. If a subject shows a worsening or the pain intensity score for the respective visit is missing then the subject will be considered a pain non-responder for the respective visit. A logistic regression model at Week 12 and Week 26 will be fitted to the data, including the covariate baseline pain intensity score, and the factors geographic region, and treatment as fixed effects. Model-based parameter estimates, standard errors, 95% confidence intervals, and p-values for the odds ratio at Week 12 and Week 26 between 400 mg neridronic acid and placebo will be tabulated.

The analysis of pain response to treatment will include a cumulative responder analysis at Week 12, Week 26, and Week 52, where responder rates will be calculated for different percentage thresholds for decrease from baseline in average pain intensity.

Dynamic mechanical allodynia

The change from baseline in the DMA will be analyzed using a similar model as for average pain intensity. Only subjects with allodynia at baseline, i.e., a DMA score greater than 0 on the 0 to 10 NRS, will be included in the analysis.

Pressure pain threshold

The change from baseline in the ratio of the PPT in the affected limb to the PPT in the unaffected limb for the thenar muscle/abductor hallucis muscle will be analyzed using a similar model as for average pain intensity. Only subjects with deep somatic pain (PPT ! 300 kPa) in the affected limb at baseline will be included in the analysis.

Edema

The change from baseline in edema will be analyzed using a similar model as for average pain intensity. Only subjects with presence of the CRPS sign “asymmetric edema” at baseline will be included in the analysis.

1.5.3.3 Missing data handling

Diligent attempts will be made to limit the amount of missing data in the primary efficacy endpoint. Efforts will be made to follow-up subjects who discontinue treatment and to collect the primary efficacy endpoint for the statistical analysis.

The primary analysis using the MMRM is based on the missing-at-random (MAR) assumption. For the treatment policy or de facto estimand, the MAR assumption is justified for neridronic acid owing to the long half-life in bone and the anticipated persistent effect over the 12-week trial period. It can be assumed that the effect of neridronic acid continues after the treatment period is completed, and it also persists after the treatment period regardless of trial completion or early discontinuation. Therefore, the response of discontinued subjects will not change if the subjects continue to receive the stable therapy that they receive during the 12-week trial period up to Visit 8. If subjects change their treatment after discontinuation from the trial, it is nevertheless reasonable to assume that their response is not significantly altered as there are currently no established effective treatments. Hence, the MAR assumption is considered a plausible missingness mechanism for the primary estimand in the case of neridronic acid.

The MAR assumption cannot be verified based on data observed in the trial. Deviations from MAR cannot be excluded and several plausible missing-not-at-random (MNAR) assumptions will be investigated to assess their impact. MNAR assumptions will be defined via PMMs specifying the distribution of missing values, e.g., for subjects discontinuing before the end of the trial. Plausible PMMs for the primary estimand are placebo multiple imputation (PMI) and the delta shift method.

Placebo multiple imputation is a reference-based approach based on the copy reference method. It models the means of missing values in the active arm based on the means observed in the placebo arm (reference arm). The method assumes that the response of discontinued subjects in the active arm gradually approaches the response in the placebo arm and eventually no effect of neridronic acid persists after a subject discontinues. For neridronic acid this appears conservative in light of the anticipated persistent effect.

The delta shift method models the means of missing values in the active arm by adding a pre-specified value Δ to the observed means in the active arm. The method includes a tipping point analysis, which is defined as the delta that must be added in order to overturn conclusions from the primary analysis from statistically significant to statistically insignificant. The method assumes that discontinued subjects in the active arm have higher pain compared to subjects who stay in the trial. Again this seems conservative if persistence of effect can be assumed for neridronic acid.

Overall, the 2 PMMs can be considered more conservative than MAR because they model missing pain intensity scores in the active arm using higher mean values than the means actually observed, whereas the placebo arm is not changed. In this way, neridronic acid is effectively penalized under these assumptions.

In summary, for neridronic acid the MAR assumption seems to be the most plausible missingness assumption for analyses estimating the primary estimand. It will be supplemented by sensitivity

analyses based on MNAR assumptions representing plausible and reasonably conservative deviations from MAR.

1.5.3.4 Confirmatory testing strategy for secondary endpoints

A confirmatory testing procedure will be used for testing of the superiority of neridronic acid 400 mg versus placebo with respect to the primary and selected secondary efficacy endpoints (change from baseline to Week 26 in the average pain intensity, change from baseline to Week 12 in the pain intensity level of DMA, change from baseline to Week 12 in the PPT ratio, and change from baseline to Week 12 in the ratio of figure of eight measurements).

First, the primary endpoint will be tested at a one-sided level $\alpha = 2.5\%$. If the first test is statistically significant, the 4 secondary endpoints will be tested in a second stage.

To control for the family-wise type I error rate at the one-sided 2.5% level, a hybrid Hochberg-Hommel step-up procedure (hybrid-0 procedure in Gou et al. 2014) will be applied. The testing procedure uses the ordered p-values $p_{(1)} \geq p_{(2)} \geq p_{(3)} \geq p_{(4)}$. At first, if the largest p-value $p_{(1)} \leq \alpha$, then all 4 hypotheses are rejected. Otherwise the associated null hypothesis $H_{(1)}$ is accepted and testing proceeds to the next step. In general, at Step $i = 2, \dots, 4$, if $p_{(i)} \leq c_i \alpha$, then any hypothesis with p-value $\leq d_i \alpha$ will be rejected and testing stops; otherwise the null hypothesis $H_{(i)}$ and testing continues at the next step. At Step 4, the null hypothesis $H_{(4)}$ is rejected if $p_{(4)} \leq \alpha/4$; otherwise $H_{(4)}$ is accepted. The constants used in the testing procedure are defined by $c_i = (i+1)/(2i)$ and $d_i = 1/i$ and are given in the table below.

i	1	2	3	4
c_i	1	3/4	2/3	5/8
d_i	1	1/2	1/3	1/4

This semiparametric multiple testing procedure controls the family-wise error rate in the strong sense if the test statistics follow a multivariate normal distribution with non-negative correlation coefficients (Gou et al. 2014) which can be assumed for the investigated 4 efficacy endpoints.

1.5.3.5 Subgroup analyses

Subgroup analyses may be done if appropriate and will be specified in the statistical analysis plan.

1.5.3.6 Pooling of sites

Individual sites will be pooled by geographic region.

1.5.3.7 Interim analysis

An interim analysis is planned after a combined total of approximately 80 subjects in the two Phase III trials, KF7013-02 and KF7013-04, have completed Week 12 of treatment and the required data is available in the databases. The interim analysis is for futility only and will be non-binding. The futility criterion will be based on the unblinded comparison of the primary endpoint and will be calculated using identical methods as for the final analysis. If the observed difference in the means of $\mu_{400} - \mu_0$ is ≥ -0.3 points on the NRS, the null hypothesis will not be rejected and the recommendation will be to stop both trials. The interim analysis will be performed by an independent statistical analysis unit not otherwise involved in the conduct of the trial and the result will only state the recommendation to stop or continue the Phase III program. No unblinded

information will be disseminated to the trial teams. Pending recruitment rates of both trials, it may be decided to forgo the interim analysis or conduct it at a different point in time. As the interim analysis will be for futility only, no inflation of the type I error will occur.

1.6 Pharmacometric analyses

Sparse pharmacokinetic sampling is performed in this trial. A previously developed population pharmacokinetics model will be updated using the plasma concentration-time data collected in this trial.

An exploratory evaluation of the potential relationships between neridronic acid exposure levels and the primary efficacy endpoint will be performed.

Modeling and simulation analyses will be performed by sponsor personnel or by authorized sponsor delegates. Details will be described in pharmacometric analysis plans.

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	Enrollment Period	Treatment Period A					Follow-up Period 1														
		Visit 2	Visit 3 ^b	Visit 4 ^b	Visit 5 ^b	Visit 6	Visit 7	Visit 8 ^c	Visit 9	Visit 10											
		Day 1	Day 4 (±1 day)	Day 7 (±1 day)	Day 10 (±1 day)	Day 15/ Week 2 (±2 days)	Day 43/ Week 6 (±3 days)	Day 85/ Week 12 (+7 days)	Day 113/ Week 16 (±4 days)	Day 155/ Week 22 (±4 days)											
Trial procedure	Visit 1 ^a																				
Check trial discontinuation criteria	Day -60 to Day -8	X	X	X	X	X				X	X				X	X					X
Check IMP suspension criteria ^s		X	X	X	X																
Administer IMP ^t		X	X	X																	
Ask the subject to record the average, worst, and current pain on the tablet computer at the site ^y		X									X	X			X	X					X
Measure edema, DMA, PPT, and AROM ^{aa}		X									X	X			X	X					
Ask the subject to complete the EQ-5D-5L		X																			
Ask the subject to complete the PROMIS-29 profile		X									X	X			X	X					X ^z
Ask the subject to complete the PROMIS-EDDEP39		X									X	X			X	X					
Ask the subject to complete the 6 neuropathic questions of the SF-MPQ-2		X									X	X			X	X					
Ask the subject to complete the PCS		X									X	X			X	X					
Ask the subject to complete the PSEQ		X									X	X			X	X					
Ask the subject to complete the PGI-S		X									X	X			X	X					X

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	Enrollment Period	Treatment Period A				Follow-up Period 1				
		Visit 2	Visit 3 ^b	Visit 4 ^b	Visit 5 ^b	Visit 6	Visit 7	Visit 8 ^c	Visit 9	Visit 10
Trial procedure	Visit 1 ^a	Day 1	Day 4 (±1 day)	Day 7 (±1 day)	Day 10 (±1 day)	Day 15/ Week 2 (±2 days)	Day 43/ Week 6 (±3 days)	Day 85/ Week 12 (+7 days)	Day 113/ Week 16 (±4 days)	Day 155/ Week 22 (±4 days)
Ask the subject to complete the WPAI: CRPS ^u		X						X		
Collect information for medical resources utilization and health economics ^u		X						X		
Take blood for pharmacokinetic evaluation ^v		X	X	X	X	X				
Take blood for bone turnover marker evaluation ^w		X				X	X	X		X
Take blood for sIL-2R testing		X						X		
Take blood for pharmacogenetic testing ^x		X								
Take blood for omics testing ^x		X						X		
Ask the subject to complete the PGIC							X	X	X	X

a) The Enrollment Period consists of an Enrollment Visit (Visit 1) prior to Day -7 and a baseline pain assessment phase from Day -7 to Day -1 during which subjects will report pain intensity ratings in the electronic diary. These pain intensity ratings will be used to calculate the baseline pain intensity score. Additional visits are allowed during the Enrollment Period to confirm normal laboratory values or ensure protocol targets for vitamin D (for details of repeat testing, see Section 1.3.2). If the Enrollment Period exceeds 30 days, determination of hematology and clinical chemistry parameters should be repeated to confirm there is no major change in the subject's overall health status prior to allocation.

aa) Edema will only be measured in subjects reporting asymmetric edema as part of the assessment of the signs and symptoms of CRPS at baseline (Visit 2). The AROM will only be measured in subjects reporting decreased AROM as part of the assessment of the signs and symptoms of CRPS at baseline (Visit 2).

b) Infusion visits should be separated by 3-day intervals to the extent possible (i.e., Day 1, Day 4, Day 7, and Day 10). Infusion visits on consecutive days are not allowed. The full dosing period must not exceed 21 days from the first infusion (Visit 2). To facilitate scheduling, the interval between infusion visits may be adapted, provided the 21 day time

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- period is not exceeded and discontinuation criteria can be assessed. In case of suspension of treatment due to a suspected safety concern or a visit scheduling difficulty, resumption of treatment is allowed upon resolution of findings, with sponsor agreement. In case of interruption or suspension of treatment, the first follow-up visit (Visit 6) should be scheduled at 4 days (± 2 days) after the last infusion visit. All subsequent visits must remain as originally scheduled relative to Visit 2 (e.g., Visit 7 occurs at 42 days [6 weeks] ± 3 days after Visit 2). No more than 4 infusions are allowed in Treatment Period A; any partial infusion (exceeding 20 mL) must be counted as 1 infusion.
- bb) Compliance assessment for electronic diary not required at Visit 1.
 - c) Visit 8 must not occur prior to Day 85 in order for the subjects to have complete electronic diary data through Week 12 for the calculation of the primary endpoint.
 - cc) Training on electronic diary as, from Week 12, the electronic diary will ask for weekly assessments of pain intensity.
 - d) The specific informed consent form for pharmacogenetic and omics sampling should preferably be signed at Visit 1, but has to be signed at the latest at Visit 2 before the sample is taken.
 - e) Demographic data will include the date of signing the informed consent form, sex, race/ethnicity, age, height, and body mass index.
 - f) History of CRPS includes the date, location, and type of precipitating event (including any information on whether there was a major nerve injury); date of onset of symptoms; date of prior CRPS diagnosis; specific location of signs and symptoms where the diagnostic criteria were applied, and information on any other/prior occurrence of CRPS or other body regions considered to be affected by CRPS.
 - g) Dental history will include: date of last dental visit; dental extractions and other invasive dental surgery in the past 3 months prior to the Enrollment Visit; current evidence of dental or periodontal disease, gum injury due to dentures, or other dental history that may pre-dispose to risk of medication-related osteonecrosis of the jaw.
 - h) After Visit 1, record any changes from the prior assessment.
 - i) At Visit 2 to Visit 5, vital signs will be taken prior to infusion and after infusion.
 - j) All ECGs will be recorded in triplicate. For Visit 2 to Visit 5, triplicate ECGs will be recorded twice: at least 15 minutes prior to the infusion and at least 15 minutes after the infusion.
 - k) Dose and dosing frequency data must be recorded.
 - l) Subjects should be queried for any events occurring since the prior visit; any events noted at Visit 1 should be documented as medical history or as part of physical examination results.
 - m) For women of child-bearing potential, a negative dipstick urine pregnancy test result must be obtained prior to each infusion. Additional pregnancy tests to those specified may be performed if required by local law or regulations.
 - n) Signs and symptoms of CRPS will be assessed at Visit 1 to confirm the diagnosis of CRPS according to the Budapest clinical criteria. Budapest criteria for ongoing, disproportionate pain and a lack of other diagnosis that better explains the signs and symptoms must also be confirmed at Visit 1. Assessments of signs and symptoms of CRPS at all subsequent visits will use symptom recall for the past 48 hours for the determination of the CRPS Severity Score.
 - o) Vitamin D and calcium supplements will be dispensed to subjects for use during the trial; subjects who are receiving appropriate doses of these supplements may continue without requirement for additional supplementation.

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- p) Compliance with inclusion and exclusion criteria must be confirmed before allocation to IMP. At Visit 2, the baseline average pain intensity score must be confirmed prior to allocation by checking the electronic diary, which will provide an automatic calculation. A baseline average pain intensity score of at least 4 on the 11-point NRS is required. A subject who has not met average baseline pain intensity requirements (at least 4 average pain intensity ratings) due to lack of compliance with the electronic diary may be rescheduled for Visit 2 (1 time only), with appropriate re-training to ensure compliance with use of the electronic diary. Subjects who do not meet eligibility criteria due to an inadequate baseline average pain intensity score (less than 4 on the NRS) will be excluded from the trial.
- q) The electronic diary is to be returned at Visit 17 or at the Early Termination Visit in the case of early discontinuation from the trial.
- r) Allocation must be performed using the interactive response technology system.
- s) Subjects must be assessed prior to each infusion and IMP should be suspended if a suspension criterion is met. This includes assessment for signs and symptoms of ocular inflammation, signs of proteinuria, and signs of dehydration. Subjects must be well hydrated prior to the start of infusions.
- t) All baseline measurements (including blood sampling for hematology, clinical chemistry, urinalysis; ECG; vital signs; physical examination) must be completed before the start of the first infusion of IMP. Investigational medicinal product must be diluted in 500 mL saline and administered by slow intravenous infusion (the infusion time must be at least 240 minutes [up to a maximum of 260 minutes]).
- u) At US sites only.
- v) For Visit 2 and Visit 5, 1 blood sample for pharmacokinetic evaluation should be taken between 5 minutes and 10 minutes prior to the start of the infusion, 1 blood sample 120 minutes after the start of the infusion, and 1 blood sample 60 minutes after the end of the infusion.
- For Visit 3 and Visit 4, 1 blood sample for pharmacokinetic evaluation should be taken between 5 minutes and 10 minutes prior to the start of the infusion and 1 blood sample between 5 minutes and 10 minutes after the end of the infusion.
- Blood samples for pharmacokinetics must be taken from a limb different from that used for the infusion and must not be taken from the infusion line.
- At Visit 6, the sample can be taken at any time point during the visit.
- w) Blood samples for bone turnover markers (C-terminal telopeptide of type I collagen, bone alkaline phosphatase, and procollagen type I amino-terminal propeptide) should be obtained in the morning after an overnight fast.
- x) The blood sample for pharmacogenetic and omics testing will be collected in consenting subjects.
- y) Worst and average pain intensity ratings will be based on a 24-hour recall period.
- z) Only the pain intensity question (question number 29, GLOBAL07) of the PROMIS-29 profile should be recorded.
- AROM = active range of motion, β -HCG = beta-human chorionic gonadotropin, CRPS = complex regional pain syndrome, DMA = dynamic mechanical allodynia, ECG = electrocardiogram, EQ-5D-5L = EuroQol-5 Dimension-5 level, IMP = investigational medicinal product, NRS = numerical rating scale, omics = a generic term referring to analysis techniques like pharmacogenetics, genomics, epigenetics, transcriptomics, proteomics, metabolomics, PCS = Pain Catastrophizing Scale, PGIC = Patient Global Impression of Change, PGI-S = Patient Global Impression of Severity, PPT = pressure pain threshold, PROMIS-29 profile = Patient-Reported Outcomes Measurement Information System (PROMIS[®])-29 profile version 2.0, PROMIS-EDDEP39 = Question EDDEP39 of the PROMIS Item Bank version 1.0 – Emotional Distress – Depression,

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PSEQ = Pain Self Efficacy Questionnaire, SF-MPQ-2 = Short-Form McGill Pain Questionnaire 2, sIL-2R = soluble interleukin-2 receptor, WPAI = Work Productivity and Activity Impairment.

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1.7.2 Visit 11 to Visit 17

	Follow-up Period 2						
	Treatment Period B (only subjects meeting the criteria to continue into Treatment Period B)				Treatment Period B		
	Visit 11 ^a	Visit 12 ^b	Visit 13 ^b	Visit 14 ^b	Visit 15	Visit 16	Visit 17 ^c
Trial procedure	Day 183/ Week 26 (+7 days)	Day 186 (±1 day)	Day 189 (±1 day)	Day 192 (±1 day)	Day 197/ Week 28 (+7/-2 days)	Day 253/ Week 36 (±7 days)	Day 365/ Week 52 (+7 days)
Record physical examination outcome ^d	X						X
Record body weight	X						X
Record vital signs ^e	X	X	X	X	X	X	X
Record 12-lead ECG ^f	X ^s	X	X	X	X		X
Record concomitant medications and therapies ^g	X	X	X	X	X	X	X
Assess further need of concomitant treatment for CRPS (in particular opioids), including decreases in dose or frequency as applicable	X					X	
Record adverse events ^h	X	X	X	X	X	X	X
Take blood for safety laboratory testing	X	X	X	X	X	X	X
Collect urine for quantitative urinalysis at the central laboratory	X	X	X	X	X	X	X
Perform dipstick urinalysis	X	X	X	X	X	X	X

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	Follow-up Period 2						
	Treatment Period B (only subjects meeting the criteria to continue into Treatment Period B)			Additional visits only for subjects going into Treatment Period B			
	Visit 11 ^a	Visit 12 ^b	Visit 13 ^b	Visit 14 ^b	Visit 15	Visit 16	Visit 17 ^c
Trial procedure	Day 183/ Week 26 (+7 days)	Day 186 (±1 day)	Day 189 (±1 day)	Day 192 (±1 day)	Day 197/ Week 28 (+7/-2 days)	Day 253/ Week 36 (±7 days)	Day 365/ Week 52 (+7 days)
Perform semi-quantitative dipstick urinalysis for urinary ACR	X ^s	X	X	X			
Perform a urine β-HCG pregnancy test ⁱ	X ^s	X	X	X			X
Perform urine drugs of abuse testing	X ^s						
Complete the assessment of the signs and symptoms of CRPS ^j	X ^s					X	X
Re-allocate to IMP ^k	X ^s						
Check trial discontinuation criteria	X	X	X	X	X	X	
Check IMP suspension criteria ^l	X ^s	X	X	X			
Administer IMP ^m	X ^s	X	X	X			
Ask the subject to record the average, worst, and current pain on the tablet computer at the site ^r	X ^r	X	X	X	X	X	X
Measure edema, DMA, PPT, and AROM ^t	X					X	X
Ask the subject to complete the EQ-5D-5L	X					X	X

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	Follow-up Period 2						
	Treatment Period B (only subjects meeting the criteria to continue into Treatment Period B)				Treatment Period B		
	Visit 11 ^a	Visit 12 ^b	Visit 13 ^b	Visit 14 ^b	Visit 15	Visit 16	Visit 17 ^c
	Day 183/ Week 26 (+7 days)	Day 186 (±1 day)	Day 189 (±1 day)	Day 192 (±1 day)	Day 197/ Week 28 (+7/-2 days)	Day 253/ Week 36 (±7 days)	Day 365/ Week 52 (+7 days)
Trial procedure							
Ask the subject to complete the PROMIS-29 profile	X				X	X	X
Ask the subject to complete the PROMIS-EDDEP39	X					X	X
Ask the subject to complete the 6 neuropathic questions of the SF-MPQ-2	X				X	X	X
Ask the subject to complete the PCS	X					X	X
Ask the subject to complete the PSEQ	X					X	X
Ask the subject to complete the PGI-S	X				X	X	X
Ask the subject to complete the WPAI: CRPS ⁿ	X					X	X
Collect information for medical resources utilization and health economics ⁿ	X					X	X
Take blood for pharmacokinetic evaluation ^o	X ^s	X	X	X	X		
Take blood for sIL-2R testing	X						
Take blood for omics testing ^u	X						
Take blood for bone turnover marker					X	X	X

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	Follow-up Period 2						
	Treatment Period B (only subjects meeting the criteria to continue into Treatment Period B)						
	Visit 11 ^a	Visit 12 ^b	Visit 13 ^b	Visit 14 ^b	Visit 15	Visit 16	Visit 17 ^c
Trial procedure	Day 183/ Week 26 (+7 days)	Day 186 (±1 day)	Day 189 (±1 day)	Day 192 (±1 day)	Day 197/ Week 28 (+7/-2 days)	Day 253/ Week 36 (±7 days)	Day 365/ Week 52 (+7 days)
evaluation ^p							
Ask the subject to complete the PGIC	X				X	X	X
Check the criteria to continue into Treatment Period B ^q	X						
Training and compliance assessment for electronic diary	X	X	X	X	X	X	X ^v
Collect electronic diary							X

If Visit 11 is not performed on Day 183, Visit 12 to Visit 15 should proceed in accordance with the originally scheduled time windows relative to Visit 11.

a) Visit 11 must not occur prior to Day 183, to ensure a full 6 months of follow-up for all subjects.

b) Infusion visits should be separated by 3-day intervals to the extent possible (i.e., Day 183, Day 186, Day 189, and Day 192). Infusion visits on consecutive days are not allowed. The full dosing period must not exceed 21 days from the first infusion of Treatment Period B (Visit 11). To facilitate scheduling, the interval between infusion visits may be adapted, provided the 21 day time period is not exceeded and discontinuation criteria can be assessed. In case of suspension of treatment due to a suspected safety concern or a visit scheduling difficulty, resumption of treatment is allowed upon resolution of findings, with sponsor agreement. In case of interruption or suspension of treatment, the first follow-up visit (Visit 15) should be scheduled at 4 days (±2 days) after the last infusion visit of Treatment Period B. All subsequent visits must remain as originally scheduled relative to Visit 11. No more than 4 infusions are allowed in Treatment Period B; any partial infusion (exceeding 20 mL) must be counted as 1 infusion.

c) Visit 17 must not occur prior to Day 365, to ensure that the subjects are followed up for a full 12 months.

d) After Visit 1, record any changes from the prior assessment.

e) At Visit 11 to Visit 14, vital signs will be taken prior to infusion and after infusion.

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- f) All ECGs will be recorded in triplicate. For Visit 11 to Visit 14, triplicate ECGs will be recorded twice: at least 15 minutes prior to the infusion and at least 15 minutes after the infusion.
- g) Dose and dosing frequency data must be recorded.
- h) Subjects should be queried for any events occurring since the prior visit.
- i) For women of child-bearing potential, a negative dipstick urine pregnancy test result must be obtained prior to each infusion. Additional pregnancy tests to those specified may be performed if required by local law or regulations.
- j) Assessments of signs and symptoms of CRPS at all visits will use symptom recall for the past 48 hours for the determination of the CRPS Severity Score.
- k) Allocation must be performed using the interactive response technology system.
- l) Subjects must be assessed prior to each infusion and IMP should be suspended if a suspension criterion is met. This includes assessment for signs and symptoms of ocular inflammation, signs of proteinuria, and signs of dehydration. Subjects must be well hydrated prior to the start of infusions.
- m) All measurements (including blood sampling for hematology, clinical chemistry, urinalysis; ECG; vital signs; physical examination) must be completed before the start of the first infusion of IMP. Investigational medicinal product must be diluted in 500 mL saline and administered by slow intravenous infusion (the infusion time must be at least 240 minutes [up to a maximum of 260 minutes]).
- n) At US sites only.
- o) For Visit 11 and Visit 14, 1 blood sample for pharmacokinetic evaluation should be taken between 5 minutes and 10 minutes prior to the start of the infusion, 1 blood sample 120 minutes after the start of the infusion, and 1 blood sample 60 minutes after the end of the infusion.
For Visit 12 and Visit 13, 1 blood sample for pharmacokinetic evaluation should be taken between 5 minutes and 10 minutes prior to the start of the infusion and 1 blood sample between 5 minutes and 10 minutes after the end of the infusion.
- Blood samples for pharmacokinetics must be taken from a limb different from that used for the infusion and must not be taken from the infusion line.
- At Visit 15, the sample can be taken at any time point during the visit.
- p) Blood samples for bone turnover markers (C-terminal telopeptide of type I collagen, bone alkaline phosphatase, and procollagen type I amino-terminal propeptide) should be obtained in the morning after an overnight fast.
- q) Compliance with the criteria to continue into Treatment Period B must be confirmed before allocation to IMP. The pain intensity question (question number 29, GLOBAL07) of the PROMIS-29 profile has to have a value of at least 4 at Visit 11. Subjects who do not meet the criteria to continue into Treatment Period B will continue with the Follow-up Period 2.
- r) Worst and average pain intensity ratings will be based on a 24-hour recall period.
- s) Only for the subjects going into Treatment Period B.
- t) Edema will only be measured in subjects reporting asymmetric edema as part of the assessment of the signs and symptoms of CRPS at baseline (Visit 2). The AROM will only be measured in subjects reporting decreased AROM as part of the assessment of the signs and symptoms of CRPS at baseline (Visit 2).

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u) The blood sample for omics testing will be collected in consenting subjects.

v) No training needed at Visit 17.

AROM = active range of motion, β -HCG = beta-human chorionic gonadotropin, CRPS = complex regional pain syndrome, DMA = dynamic mechanical allodynia, ECG = electrocardiogram, EQ-5D-5L = EuroQol-5 Dimension-5 level, IMP = investigational medicinal product, omics = a generic term referring to analysis techniques like pharmacogenetics, genomics, epigenetics, transcriptomics, proteomics, metabolomics, PCS = Pain Catastrophizing Scale, PGIC = Patient Global Impression of Change, PGI-S = Patient Global Impression of Severity, PPT = pressure pain threshold, PROMIS-29 profile = Patient-Reported Outcomes Measurement Information System (PROMIS®)-29 profile version 2.0, PROMIS-EDDEP39 = Question EDDEP39 of the PROMIS Item Bank version 1.0 – Emotional Distress – Depression, PSEQ = Pain Self Efficacy Questionnaire, SF-MPQ-2 = Short-Form McGill Pain Questionnaire 2, sIL-2R = soluble interleukin-2 receptor, WPAL = Work Productivity and Activity Impairment.

1.8 **References**

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150 (9): 604-12.

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3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

3.1 Abbreviations

Abbreviation	Explanation
β-HCG	Beta-human chorionic gonadotropin
ACR	Albumin to creatinine ratio
ANCOVA	Analysis of covariance
AROM	Active range of motion
BAP	Bone alkaline phosphatase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COMPACT	Core outcome measures for complex regional pain syndrome clinical trials
CRO	Contract research organization
eCRF	Electronic case report form
CRPS	Complex regional pain syndrome
CRPS-I/CRPS-II	Complex regional pain syndrome Type I/ Complex regional pain syndrome Type II
CTX	C-terminal telopeptide of type I collagen

Abbreviation	Explanation
DMA	Dynamic mechanical allodynia
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EFPIA	European Federation of Pharmaceutical Industries and Associations
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL-5 Dimension-5 level
FDA	Food and Drug Administration
GCP	Good clinical practice
IASP	International Association for the Study of Pain
IEC	Independent ethics committee
IL-2	Interleukin-2
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IMP	Investigational medicinal product
IRB	Institutional review board
MAR	Missing-at-random
MDMA	3,4-methylenedioxy methamphetamine, ecstasy
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
MNAR	Missing-not-at-random
NRS	Numerical rating scale
Omics	A generic term referring to analysis techniques like pharmacogenetics, genomics, epigenetics, transcriptomics, proteomics, metabolomics
PCS	Pain Catastrophizing Scale
PGIC	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PINP	Procollagen type I amino-terminal propeptide
PMI	Placebo multiple imputation
PMM	Pattern mixture model
PPT	Pressure pain threshold
PROMIS	Patient-Reported Outcomes Measurement Information System (PROMIS [®])
PROMIS-29 profile	Patient-Reported Outcomes Measurement Information System (PROMIS [®])-29 profile version 2.0
PROMIS-EDDEP39	Question EDDEP39 of the PROMIS Item Bank version 1.0 – Emotional Distress – Depression
PSEQ	Pain Self Efficacy Questionnaire
QTcF	Corrected QT interval (according to Fridericia's formula)
SAE	Serious adverse event
SF-MPQ-2	Short-Form McGill Pain Questionnaire 2

Abbreviation	Explanation
sIL-2R	Soluble interleukin-2 receptor
SOP	Standard operating procedure (used as synonym for all procedural documents)
TEAE	Treatment emergent adverse event
USP	United States Pharmacopeia
VAS	Visual analog scale
WPAI	Work Productivity and Activity Impairment

Système International d'Unités units and standard hematological and biochemical abbreviations are not listed.

3.2 Definition of terms

Term	Definition
Allocated subjects	Enrolled subjects who are assigned to IMP.
Applicable regulatory requirement(s)	Any law(s) and regulation(s) addressing the conduct of clinical trials of IMPs of the jurisdiction where the trial is conducted.
CRPS Type I	Occurs after a minor or major tissue injury without clinical signs of major peripheral nerve injury.
CRPS Type II	Occurs after an injury with clinical signs of major peripheral nerve injury.
End of the trial	The trial-related end of the trial is defined as the date of last subject out. The subject-related end of trial is defined as date of last contact with the subject according to the protocol.
Enrolled subjects	Subjects who signed an informed consent form.
Enrollment failures	Enrolled subjects who were not allocated to IMP.
First subject allocated	First subject that was allocated to IMP.
First subject in	Date of first enrolled subject.
Investigational medicinal product	A generic term describing the preparation(s) under investigation in this trial, i.e., neridronic acid and placebo.
Last subject out	Date of last contact with the last subject according to the protocol.
Patient	Person under a physician's care for a particular disease or condition.
Screened subjects	Screened subjects are subjects undergoing screening. Screening is any activity concerning subjects who could potentially be enrolled into the trial before the informed consent form is signed.
Subject	Individual who participates in a clinical trial (healthy person or patient), either as recipient of an IMP or as control.
Treated subjects	Subjects with at least 1 administration of IMP.

Use of the terms “must” and “should”

When “must” is used, the action/item is always mandatory. Non-compliance with this instruction constitutes a protocol deviation.

When “should” is used, the action/item is recommended but not mandatory. Non-compliance with this instruction does not constitute a protocol deviation.

4 ETHICS

This trial will be conducted according to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, good clinical practice (GCP), and applicable regulatory requirements.

This trial will be registered in public registries according to the applicable laws and requirements.

4.1 Independent ethics committees or institutional review boards

The relevant independent ethics committees (IECs) or institutional review boards (IRBs) for this trial will be provided with all documents required to fulfill their responsibilities. Any updates thereof will be provided according to GCP and applicable regulatory requirements.

Trial activities will only start when approval from the relevant IECs or IRBs is available.

Documentation of all involved IECs or IRBs will be maintained according to GCP and applicable regulatory requirements.

4.2 Subject information and informed consent

Before any trial-related procedure will be performed, freely given informed consent must be obtained.

The informed consent discussion, the information sheet (if used) and the informed consent form provided to subjects must adhere to GCP and applicable regulatory requirements. The informed consent discussion with the subject must be performed by the principal investigator or an appropriately trained delegate. The information sheet and informed consent form agreed with the sponsor must be used. Prior to use, these documents must be approved by the relevant IECs or IRBs.

Subjects must be informed as soon as possible if new information becomes available that may be relevant to their willingness to continue participation in the trial. The communication of this information must be documented.

Collection of blood samples for storage and pharmacogenetic and omics (a generic term referring to analysis techniques like pharmacogenetics, genomics, epigenetics, transcriptomics, proteomics, metabolomics) assessment is optional for trial subjects.

A separate informed consent for the collection of blood samples for pharmacogenetic and omics testing will be obtained in addition to the standard informed consent for the clinical trial. Failure to provide this additional consent will not affect the subject's ability to participate in the clinical trial.

A copy of the signed and dated informed consent form will be given to the subject and the original will be filed in the investigator's site file.

Subjects who give consent for pharmacogenetic and omics testing may reconsider and decide to withdraw their consent. Subjects will be informed during informed consent that withdrawal of consent requires them to contact the investigator. The investigator will then notify the sponsor in writing of the subject's decision, and the sponsor will instruct the bio-banking facility to destroy the stored sample(s) of the subject. The destruction of the subject's sample(s) will be documented by the sponsor and in the bio-banking facility records. All pharmacogenetic and omics data already

evaluated prior to the withdrawal of consent will continue to be reported in completed or ongoing pharmacogenetic and omics analyses, but will be excluded from all subsequent analyses.

The subjects must be informed that any compound-related discoveries resulting from the pharmacogenetic and omics testing and analyses are the property of the sponsor. They may be used by the sponsor for commercial purposes.

4.3 Informing the subject's healthcare provider

In countries where applicable, and only if the subject agrees in writing in the informed consent form and is treated by a healthcare provider, e.g., general practitioner, the subject's healthcare provider should be informed about the subject's participation in the trial at trial enrollment. The healthcare provider should be informed about the trial code, the principal investigator's name, and a contact (telephone) number at the trial site.

Any communication with the healthcare provider must be documented in the subject's medical records or the investigator's site file.

5 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

5.1 Investigators and trial site personnel

5.1.1 Investigators

There must be an investigator at each trial site.

If the trial is conducted by a team of individuals at the trial site, the investigator leading and responsible for the team is called the principal investigator.

All persons assigned responsibility as principal investigator must sign a declaration of their responsibilities and their agreement to this protocol before any trial-related procedure is performed.

Curriculum vitae and/or other relevant documents confirming the current qualification of the investigators must be provided to the sponsor. This should include any previous training in the principles of GCP, experience obtained from work with clinical trials, and experience with subject care.

Documentation of all involved investigators must be maintained according to GCP and applicable regulatory requirements.

In different countries, there may be country-specific terminology used for the investigator role.

An international coordinating investigator will be defined who is responsible for the coordination of principal investigators at multiple trial sites in multiple countries.

Documentation of all responsibilities assigned to the country-specific coordinating investigators/international coordinating investigator must be maintained according to GCP and applicable regulatory requirements.

5.1.2 Trial site personnel assigned trial-related duties

The principal investigator may define appropriately qualified personnel at a trial site to perform significant trial-related procedures and/or to make trial-related decisions under his/her supervision. In this case, the principal investigator must maintain a signed list of the persons to whom they delegate significant trial-related duties/responsibilities; the delegated trial-related duties/responsibilities must be specified in the list.

When personnel or responsibility changes are made, the principal investigator must ensure that the relevant documentation is updated before any trial-related activities are performed.

Documentation of all involved trial site personnel performing significant trial-related procedures and/or making trial-related decisions must be maintained according to GCP and applicable regulatory requirements.

5.2 Contract research organizations

Contract research organizations (CRO; commercial, academic or other, e.g., central laboratory facilities, trial supply management provider, electronic clinical outcomes assessment tool provider) may be contracted by the sponsor to perform trial-related duties and functions. The extent of the delegation must be documented. All involved CROs will be required to have implemented quality control and quality assurance processes, and to support the sponsor's quality control and quality assurance measures.

Documentation of all involved CROs must be maintained according to GCP and applicable regulatory requirements. Documentation of any delegation of responsibilities to CROs must be maintained in the trial master file.

5.3 The sponsor and sponsor's personnel

The trial sponsor listed on the title page accepts the responsibilities of the sponsor according to GCP and applicable regulatory requirements.

The sponsor must designate appropriately qualified personnel to advise on trial-related topics. The trial site will be provided with contact details for these personnel before any trial-related procedure is performed.

A list of key sponsor personnel involved in the preparation of this protocol and the conduct of the trial, including their full names, titles, roles, and responsibilities, must be maintained.

A list of key personnel contracted by the sponsor and involved in the conduct of the trial including their full names, addresses, and responsibilities, must be maintained.

6 INTRODUCTION AND TRIAL BACKGROUND

6.1 Introduction

Complex regional pain syndrome is a severe and frequently chronic disabling condition that can develop after a minor injury, such as a fracture or sprain, usually in a distal extremity (hand, wrist, ankle, and foot). Complex regional pain syndrome is characterized by disproportionate pain,

relative to the inciting event, and signs and symptoms related to sensory, vasomotor and sudomotor abnormalities, trophic changes (abnormal skin, hair, and nails), and impaired motor function in the affected limb (Harden et al. 2010a). There are currently no Food and Drug Administration (FDA) approved pharmacological treatments for CRPS, and patients are underserved due to a poor understanding of the pathophysiological processes and lack of evidence for effective treatments (Harden et al. 2013; Goebel 2013; Bruehl 2015).

Randomized placebo-controlled trials of bisphosphonates in patients with CRPS suggest that these agents are efficacious for treatment of pain and other symptoms associated with this syndrome (Brunner et al. 2009; Cossins et al. 2013; O'Connell et al. 2013; Varenna et al. 2013; Wertli et al. 2014). Since bisphosphonates act to suppress osteoclastic bone resorption, it is likely that bone pathology plays a role in the evolution and maintenance of CRPS Type I (CRPS-I; Gatti et al. 2016), although other mechanisms may be involved (Varenna et al. 2013). Evidence of osteopenia and increased uptake of radiolabeled bisphosphonate tracer (observed during bone scintigraphy) in the affected limb(s) of patients with CRPS provides support for this hypothesis. Therefore, the present trial with a total dose of neridronic acid 400 mg is designed to obtain efficacy and safety information to support the potential broader use of neridronic acid to address a major unmet medical need in patients with CRPS.

6.2 Background to the IMP

Neridronic acid is an alkyl-aminobisphosphonate with a chemical structure and potency similar to that of pamidronate (Gatti et al. 2013). Neridronic acid has been studied in subjects with Paget's disease of bone, osteogenesis imperfecta, hypercalcemia, and osteoporosis and has been marketed in Italy under the tradename NERIXIA[®] for treatment of osteogenesis imperfecta since 2002 and for Paget's disease since 2006. In 2014, NERIXIA received market authorization for treatment of CRPS in Italy.

Neridronic acid is currently being investigated for the treatment of CRPS.

6.3 Relevant non-clinical and clinical data

For a detailed summary of relevant non-clinical and clinical experience, see the current edition of the neridronic acid investigator's brochure.

In a pilot trial of neridronic acid, 9 subjects with CRPS-I were randomized to 2, 3, or 4 infusions of 100 mg intravenous neridronic acid every 4 days in the first phase of the trial (Varenna et al. 2004). The cumulative intravenous doses of 200 mg and 300 mg were considered suboptimally effective. The 4 x 100 mg dose of neridronic acid was identified as the only regimen providing clinical improvement equivalent to 300 mg/day intravenous clodronate for 10 days (i.e., a total dose of 3000 mg) investigated in CRPS in an earlier trial (Varenna et al. 2000). Equivalence of the 400 mg cumulative dose of neridronate, based on indirect equivalence to 3000 mg clodronate, was confirmed in a second phase of the pilot trial with 18 patients.

In a multi-national, randomized, double-blind, placebo-controlled trial in patients with CRPS-I (KF7013 01; NCT02402530) total doses of 125 mg and 250 mg neridronic acid administered as 4 intravenous infusions over a period of 10 days were well tolerated but did not differentiate

significantly from placebo on the primary efficacy parameter, confirming that a higher dose would be required for the effective treatment of CRPS.

In a multi-site, placebo-controlled trial of intravenous neridronic acid in 82 subjects with CRPS-I receiving 400 mg of neridronic acid, administered as four 2-hour infusions of 100 mg on Day 1, Day 4, Day 7, and Day 10, a statistically significantly greater percentage of subjects experienced at least 50% decrease in pain intensity at 40 days after the first infusion compared with placebo (73.2% for neridronic acid versus 32.5% for placebo [treatment difference: 40.7%; 95% confidence interval: 18.7%, 59.5%]; $p = 0.0003$). Secondary endpoints, including change from baseline in pain intensity, pain evoked by passive motion, edema, AROM, hyperalgesia, and allodynia, also showed significant improvements (Varena et al. 2013). There were no serious or severe adverse events in the neridronic acid treatment group. The most frequent adverse events were arthralgia, fever, and headache, consistent with the acute phase reaction.

6.4 Trial rationale

Grünenthal is currently developing intravenous neridronic acid for treatment of CRPS.

The aim of the current trial is to investigate the efficacy, safety, and tolerability of neridronic acid administered as 4 intravenous infusions of neridronic acid 100 mg, resulting in a total dose of 400 mg, in subjects with CRPS. This pivotal trial is intended to be an integral part of the overall efficacy and safety assessment of neridronic acid for the treatment of subjects with CRPS and to support product registration.

Additional aims are to assess the safety and tolerability of initial dosing with neridronic acid for up to 12 months, to assess the need for further treatment after 6 months, and to describe the effect of an additional treatment cycle of 4 additional infusions of 100 mg of neridronic acid.

7 TRIAL OBJECTIVES AND ENDPOINTS

The trial objectives and endpoints are given in Section 1.2.

The pain intensity score used for the primary endpoint will be calculated from average pain intensity ratings, assessed once daily in the electronic diary and referring to the CRPS-affected limb. The baseline average pain intensity score is defined as the average of the week before allocation to treatment at Visit 2 and calculated as the average of the 7 average pain intensity ratings starting in the evening of Day -7 until Day -1. A baseline pain intensity score (≥ 4 on the NRS) must be confirmed at the site prior to subject allocation (at Visit 2). Subjects who do not meet eligibility criteria due to inadequate pain (< 4 on the NRS) will be excluded from the trial.

Pain intensity scores from Week 1 through Week 12 will be calculated in a similar manner using average pain intensity ratings obtained from the electronic diary. The Week 12 pain intensity score, for evaluation of the primary outcome, will be the average of up to 7 possible ratings obtained in the 7-day period culminating with the rating obtained in the evening prior to the Week 12 visit.

Handling of missing pain ratings will be addressed in the statistical analysis plan. Compliance with the pain ratings in the electronic diary must be monitored and subjects with insufficient ratings (< 4 ratings per week for 2 weeks) should receive a reminder and undergo re-training.

During Visit 2 (Day 1), Visit 7 (Week 6), Visit 8 (Week 12), Visit 9 (Week 16), and Visit 11 (Week 26), Visit 16 (Week 36), and Visit 17 (Week 52), the subjects will be asked to record the pain intensity ratings for average, worst, and current CRPS-related pain directly on a tablet computer maintained at the site. For subjects included in Treatment Period B, the subjects will also be asked to record pain intensity rating at Visit 12, Visit 13, Visit 14, and Visit 15. Worst and average pain intensity ratings will be based on a 24-hour recall period. The pain ratings and other patient-reported outcomes from the tablet computers recorded up to Week 26 as well as DMA, edema, and PPT assessment will be used for the secondary endpoints.

8 TRIAL DESIGN

8.1 Discussion of the trial design

This is a multi-site, randomized, double-blind, placebo-controlled, 2-arm, Phase III trial of intravenous neridronic acid in subjects with CRPS.

The trial design was selected to confirm the efficacy and safety of neridronic acid in subjects with CRPS. A randomized, double-blind design was chosen to avoid selection bias and provide balance of baseline characteristics across treatment groups. Blinding is critical to minimize potential biases resulting from differences in management, treatment, or assessment of subjects, or interpretation of results that could arise as a result of subject or investigator knowledge of the assigned treatment.

Parallel-group designs are well-understood from a statistical design perspective. A crossover, randomized-withdrawal, or other design was considered unsuitable for this trial due to the very long half-life of bisphosphonates, which may persist in bone for years.

The 11-point NRS is a standard, widely used tool for the assessment of pain and is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) as a core outcome measure in chronic pain trials (Dworkin et al. 2005).

The efficacy assessments chosen for this trial reflect the core outcome measures for CRPS clinical trials (COMPACT; Grieve et al. 2017). For further details, see Section 12.10.

Semi-objective measures for frequent signs of CRPS beyond spontaneous pain (i.e., DMA, PPT edema, AROM) have also been included.

Choice of control

Use of a placebo control is considered justifiable when there are no established effective treatments for a disease or condition (ICH E10). As reflected in a recent Cochrane review of interventions for CRPS, there is no consensus for optimal management of this condition and the limited number of published trials provides only low or very low quality of clinical evidence for any intervention (O'Connell et al. 2013). In the absence of a suitable active comparator, the use of a placebo control allows for blinding and randomization to control for expectations of benefits that may occur from being in the trial. The placebo group also controls for spontaneous changes in the course of the disease. The use of placebo in this trial does not imply that subjects will be untreated, as subjects may continue to receive stable analgesic regimens during the trial as well as short-acting analgesics in case of severe pain flare related to CRPS (for details, see Section 1.4.2).

Trial design limitations

The concomitant use of pain medications in this trial, which are allowed because of the severity of the condition, may affect the sensitivity of subject-reported outcomes and the ability to detect changes in pain intensity. Therefore, it is important to emphasize the need for stable treatment during the trial at least until Week 12 to optimize assessment of the primary endpoint. Any changes in pain medications must be recorded.

Second treatment course

For those subjects not experiencing sufficient efficacy after a first treatment course with IMP as assessed at Visit 11 (Week 26), a second treatment period (Treatment Period B) in subjects with persistent pain is included to allow subjects previously on neridronic acid and on placebo to be treated with neridronic acid either for the second or the first time, respectively. The second treatment course is scheduled to occur after 26 weeks.

Subjects treated during Treatment Period B will provide data on safety and tolerability of a second treatment course as well as descriptive data on the efficacy of a second treatment course in subjects with no or insufficient response to the first treatment course as well as in subjects who lost response to the initial treatment course. Furthermore, subjects from the placebo group can receive verum treatment in Treatment Period B.

8.1.1 Rationale for the trial population

Although previous trials with neridronic acid have been performed in subjects with CRPS-I, CRPS-I and CRPS Type II (CRPS-II) are likely to share the same pathophysiological basis (Oaklander and Horowitz 2015; Bruehl 2015).

There are no known methods to objectively distinguish between CRPS-I and CRPS-II subtypes, as electromyography and nerve conduction studies have low negative predictive value and do not rule out nerve abnormalities in CRPS-I. Furthermore, pathophysiological changes in bone, the principal target for efficacy of neridronic acid, may occur in patients diagnosed with CRPS-II.

Given the uncertain distinctions between these subtypes and lack of pathologic or pharmacologic basis for restricting treatment to CRPS-I, subjects with CRPS-II will also be included in this trial.

Reports from the literature suggest better responses to treatment when subjects are treated early after onset of the first symptoms (Wertli et al. 2014). There is no consensus on an exact time window for treatment. Preliminary data from an open-label trial employing a cumulative dose of neridronic acid 400 mg (KF7013-03), suggest clinically relevant decreases in pain intensity in a subgroup of subjects with a CRPS duration ≤ 2 years. The trial population in this trial will therefore be limited to this disease duration.

Subjects must be on stable therapy prescribed for CRPS for at least 1 month prior to randomization and allocation to maximize sensitivity to detect changes in pain intensity and other efficacy outcomes. Analgesic regimens including pro re nata (as needed) opioids or other analgesics are allowed if the regimen has been prescribed as part of a stable treatment. The investigator must select subjects who are anticipated to be able to maintain a stable treatment regimen for the first 12 weeks of the trial (up to and including Visit 8). Initiation of new therapies during the trial will be prohibited. Short courses of analgesics, including opioids (unless prohibited according to Section 1.4.2.1), will be allowed to be prescribed in the event of a severe pain flare.

8.1.2 Rationale for the investigational medicinal products and the selected doses

A previous pilot trial of neridronic acid, including cumulative intravenous doses of 200 mg, 300 mg, and 400 mg, suggested that doses below 400 mg were suboptimally effective (Varenna et al. 2004).

A previous randomized, double-blind, placebo-controlled trial performed by Abiogen Pharma S.p.A. demonstrated that a 400 mg cumulative intravenous dose of neridronic acid is effective, safe, and well tolerated in subjects with CRPS-I (Varenna et al. 2013; Clinical Study Report NERI-AS001-07). As the 4 x 100 mg dose regimen used in that trial has been approved for treatment of CRPS-I in Italy, the same dose regimen was selected for investigation in this trial.

In Italy, the recommended infusion time for 100 mg neridronic acid to treat osteogenesis imperfecta and CRPS-I is 2 hours. To limit the maximum concentrations (C_{max}) in this trial to levels similar to (and unlikely to exceed) those obtained in the KF7013-01 trial, in which 62.5 mg neridronic acid was infused in 2 hours, the infusion time has been extended to 4 hours.

8.1.3 Rationale for the number and the frequency of visits/assessments

The number and frequency of visits are considered to be sufficient to ensure subject safety and meet trial objectives.

8.1.4 Background and rationale regarding pharmacogenetic and omics testing

The European Medicines Agency (EMA; 2011) and United States FDA (2013) guidance documents recommend the conduct of pharmacogenetic assessments in clinical trials during drug development (Phase I to Phase III).

Genetic factors are suggested to play a role in CRPS (de Rooij et al. 2009). To further characterize protein-coding areas, signatures, and haplotypes related to CRPS-I, potentially relevant genes together with genes of the corresponding signaling pathways will be analyzed using genotyping of a panel of pre-selected single-nucleotide polymorphisms and proteomics of proteins encoded by these genes. The aim is to identify relevant pathways and gene-phenotype associations that will allow a phenotypic characterization of CRPS pain conditions. The associated single-nucleotide polymorphisms will be related to all corresponding proteins and then further analyzed using omics methods to identify potential biomarkers. In addition, the associated single-nucleotide polymorphisms will be used to identify potential genetic predispositions to CRPS and the function of these genes in response to treatment and disease progression, including potential linked side effects.

All measurements and analyses will be described in separate pharmacogenetic and omics plans.

8.2 Benefit/risk analysis

Potential benefits to subjects participating in this trial may include a reduction in pain and other symptoms of CRPS, as well as benefits of medical supervision from being in a clinical trial.

Risks to subjects participating in this trial are primarily related to the known side effects of neridronic acid and bisphosphonates as a class, particularly those associated with intravenous administration. Although doses of up to 400 mg of neridronic acid have been administered safely in

subjects with Paget's disease or CRPS-I, most of the clinical experience for neridronic acid has been at doses of 200 mg or below. In addition to drug-specific risks, there are also the risks of the procedures used in the trial.

In order to minimize the risk for the subject, it is obligatory that the investigator becomes familiar with all sections of the current neridronic acid investigator's brochure prior to the initiation of the trial and follows the warnings and directions thereof.

The trial population described in this protocol will consist of subjects with a diagnosis of CRPS, with onset of symptoms within the last 2 years, and who are medically stable and in stable follow-up therapy for CRPS for at least 1 month prior to allocation.

Subjects will continue to receive stable therapy for CRPS. Additional pain medication may be prescribed in the event of severe pain flare, with notification of the sponsor or sponsor's representative (i.e., medical monitor). Changes in analgesic medications and other treatments for CRPS may be permitted after Week 12, following notification of the sponsor or sponsor's representative (i.e., medical monitor). After Visit 10, investigators will assess the further need of concomitant treatment for CRPS, in particular opioids, and evaluate if the dose or frequency of these treatments can be decreased, or if treatment can be stopped completely. This will help to ensure that subjects in the trial will not suffer from untreated pain and that the subject's exposure to other analgesics will be decreased or stopped if they are no longer needed. Subjects may withdraw from the trial at any time, without giving a reason and without prejudice. However, subjects who withdraw will be asked to continue follow-up visits if at all possible for the scientific integrity of the trial as well as for their own safety.

Potential risks and risk management of neridronic acid

Acute phase reaction

The most common side effects associated with parenteral administration of aminobisphosphonates are flu-like symptoms, commonly referred to as "acute phase reaction" (Reid et al. 2010; Silverman et al. 2011). Symptoms include fever, myalgia, fatigue, headache, diarrhea, arthralgia, and bone pain. These are self-limiting and usually resolve after 24 hours to 48 hours. Symptoms of the acute phase reaction typically occur following the first administration and are absent or decreased following subsequent administrations. For symptomatic management of the acute phase reaction, oral acetaminophen (paracetamol) is recommended (for details, see Section 1.4.2). Non-steroidal anti-inflammatory drugs should not be used to alleviate the symptoms of the acute phase reaction due to their potential to cause acute changes in renal function, which may confound renal safety assessments.

Ocular effects

Eye disorders have been reported with neridronic acid and appear to be associated with the acute phase reaction. These events include anterior uveitis, episcleritis, conjunctivitis and ocular pain. As severe ocular inflammation may increase the potential risk of long-term vision loss, treatment with neridronic acid will be discontinued at first signs of ocular inflammation, followed by an ophthalmologic exam.

Hypocalcemia

Aminobisphosphonates are potent inhibitors of bone turnover, and are thus associated with a risk of hypocalcemia.

The normal compensatory mechanism is an increase in parathyroid hormone, which can trigger renal absorption of calcium and vitamin D3 production in response to a decreased calcium efflux from the skeleton after bisphosphonate therapy (Polyzos et al. 2011).

Subjects with abnormal blood calcium or magnesium concentrations, a history of disorders that impair the compensatory increase in parathyroid hormone, or concomitant use of any drug with known potential to cause hypocalcemia will be excluded from the trial. Retesting of out-of-range values is permitted once during the Enrollment Period. Albumin-corrected serum calcium should be considered when serum albumin is below the normal range (e.g., <3.5 g/dL).

All subjects will be provided with supplemental calcium and vitamin D, starting from Visit 1 and continuing through to the end of the trial (for details, see Section 1.4.2). Subjects with vitamin D levels below 30 ng/mL (75 nmol/L) will receive supplementation to achieve values of at least 30 ng/mL (75 nmol/L) prior to allocation to IMP. Subjects who do not reach vitamin D levels of at least 30 ng/mL (75 nmol/L) following appropriate supplementation will be excluded from the trial.

Renal toxicity

Based on the available data for neridronic acid, there is no clinical evidence for renal safety concerns to date. Nevertheless, renal toxicity was observed in non-clinical studies of neridronic acid and is regarded as a class effect of intravenous bisphosphonates. In most cases, signs for renal toxicity following administration of other intravenous bisphosphonates were transient and reversible after discontinuation of the drug or dose adjustment. Pronounced renal toxicity is a rare event, more common in long-term use, and there is a contributing role of pre-existing renal disease as well as other factors like other medication associated with renal toxicity and dehydration.

Bisphosphonates are rapidly cleared by the kidneys, potentially leading to a high concentration in kidney tissue during and immediately after the infusion. Dose and infusion time are the main factors related to renal toxicity.

In order to mitigate the risk of renal toxicity, subjects with evidence of severe renal impairment will be excluded (for details, see exclusion criterion 1).

Taking into account that renal toxicity due to intravenous bisphosphonates is related to the maximum drug concentration achieved and not the area under the curve of drug exposure (Khosla et al. 2012), 400 mg neridronic acid will be administered as 4 infusions of 100 mg neridronic acid administered over 240 minutes at Visit 2, Visit 3, Visit 4, and Visit 5 (and Visit 11, Visit 12, Visit 13, and Visit 14 during Treatment Period B) to subjects with no or mild renal impairment.

For subjects with moderate renal impairment, the dose will be adjusted (see Section 10.2).

Due to the potential for renal toxicity with neridronic acid as with other bisphosphonates, renal safety monitoring will be implemented in this trial together with defined stopping criteria (for details, see Section 9.3.2).

Cardiovascular

Despite the ability to transiently lower calcium levels, there has been no indication to date that bisphosphonates, as a class, cause prolongation of QT interval. Neridronic acid has not been studied in dedicated safety trials to evaluate a potential effect on the QT interval. Subjects with risk factors for QT prolongation or cardiac arrhythmia, including abnormal serum potassium levels, are excluded from this trial. Subjects will undergo regular 12-lead ECG examinations throughout the trial.

Medication-related osteonecrosis of the jaw

Osteonecrosis of the jaw is a rare adverse effect of bisphosphonate therapy, most commonly reported for patients with multiple myeloma and osteolytic bone metastases receiving repeated monthly infusions for treatment of skeletal related events and bone pain. Factors that may contribute to risk of osteonecrosis of the jaw include recent tooth extraction, unhealed or infected extraction sites, dental/periodontal disease, improperly fitting dentures causing injury, and prior radiation of the head or neck.

Invasive dental procedures should be avoided during the trial; however, subjects who require emergency dental surgery during the trial should proceed with appropriate treatment including prophylactic antibiotics and frequent follow-up. Subjects should be encouraged to use good dental hygiene (daily flossing and gentle brushing) throughout the trial.

Osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections and/or local risk factors such as infection or trauma.

Atypical femoral fractures

Although a causal relationship has not been conclusively established, meta-analysis suggests there is an increased risk of atypical femoral fractures in long-term bisphosphonate users. These fractures have a low prevalence (1.1% of all femoral fractures), and the absolute risk to patients receiving bisphosphonates is low. Subjects should be advised to report any thigh, hip, or groin pain, and any patient who develops these symptoms should be evaluated for the presence of an incomplete femur fracture.

Other effects on bone

Although the potential for deleterious effects on bone following long-term treatment with bisphosphonates remains controversial to this day, no histomorphometric evidence of osteomalacia was reported at doses up to neridronic acid 250 mg in patients with Paget's disease of bone (McCloskey et al. 1987; Atkins et al. 1987), in contrast to findings following administration of the first generation bisphosphonate, etidronic acid.

Supporting the absence of any important effect on bone health, long-term neridronic acid treatment increased bone mineral density and lowered risk of clinical fracture in children and adults with

osteogenesis imperfecta. These results argue against a deleterious effect on bone mineralization due to neridronic acid.

However, the potential for deleterious effects of bisphosphonates on bone has been suggested in conditions of low bone turnover, such as renal osteodystrophy or other adynamic bone disease, although the benefit/risk profile in these conditions is unclear. In addition to exclusion of subjects with chronic kidney disease stage 4 and 5, subjects with known defects in bone mineralization or adynamic bone disease are excluded from the trial.

Pregnancy and breastfeeding

There are no adequate and well-controlled trials of neridronic acid in pregnant or lactating women. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone may be greater than into maternal bone. Therefore, neridronic acid should not be administered during pregnancy and lactation and as a result, pregnant or lactating women are excluded from participation in this trial.

Women of child-bearing potential must have a negative urine β -HCG pregnancy test at the Enrollment Visit and prior to each infusion of IMP. Trial subjects must use contraception as defined in inclusion criterion 6.

Risks related to acetaminophen and calcium and vitamin D supplementation

High doses of acetaminophen may cause hepatotoxicity and can lead to liver failure. Subjects who take acetaminophen for prevention or relief of symptoms of the acute phase reaction during the treatment periods will be reminded that the total dose must not exceed 4 g/day and that caution should be exercised since acetaminophen may be present in many over-the-counter drugs, particularly analgesic medications.

Recommended daily doses of calcium and vitamin D are lower than the tolerable upper intake level, at which there is no risk to healthy individuals (Ross et al. 2011; Rosen et al. 2012). Short courses of high doses of vitamin D are anticipated to pose no significant risk to trial participants.

General risks

Subjects will be regularly monitored for any changes in their medical status, e.g., vital signs, ECG parameters, and laboratory values, during the trial (see Section 12.1 for overall volume of blood samples).

Blood sampling may cause pain or bruise at the site where the blood is taken due to insertion of the needle. No other invasive procedure is planned. The total volume of blood to be collected and the planned sampling frequency do not pose any clear risk and are considered justifiable in the context of the trial and its duration.

Conclusion

As there are currently no FDA or EMA approvals for specific pharmacological treatments for CRPS, which is a severe pain condition with limited effective treatment options, the potential for benefit of neridronic acid is considered to outweigh the potential risk in this population. The need for controlled efficacy and safety trials of potential new treatments for CRPS justifies this trial on moral and ethical grounds.

9 SUBJECT ENROLLMENT AND TRIAL DISCONTINUATION

9.1 Subject enrollment procedure

Subjects will be screened to identify subjects who could potentially be enrolled into the trial. Potentially eligible subjects will be asked to enroll into the trial by giving written informed consent.

If required by applicable regulatory requirements, the (principal) investigator must keep suitable logs of the subject enrollment procedure.

Subjects who were enrolled in KF7013-01 but were not allocated to treatment (i.e., did not receive any treatment with IMP) or who only received placebo may be eligible if they satisfy all inclusion and exclusion criteria in Section 1.3.

Re-enrollment will be permitted (once), upon approval by the sponsor, for subjects with technical reasons for enrollment failure (e.g., inadequate time period for stabilization of treatment; inadequate time from discontinuation of a prohibited medication or treatment). No subject who received infusion of IMP, even a partial infusion, is allowed to be re-enrolled. Re-enrollment of subjects who did not meet inclusion criteria related to the diagnosis of CRPS and the baseline pain level is not allowed. Re-enrolled subjects must fulfill all inclusion and exclusion criteria in the current protocol. If a subject is re-enrolled, a new subject ID will be assigned and all enrollment procedures will be performed under the new subject ID.

9.2 Inclusion/exclusion criteria

The trial population must comply with the inclusion/exclusion criteria given in Section 1.3.

Subjects will only receive IMP if documentation is available showing that they comply with all of these criteria.

9.3 Subject discontinuation from the trial or IMP

Once a subject enrolls in this trial, whilst protecting subject safety, the trial site should make every effort to retain the subject for the planned duration of the trial.

A subject may withdraw consent at any time.

9.3.1 Subject discontinuation from the trial

All bisphosphonates have a long retention time in bone, and duration of efficacy is related to their persistent effects on bone turnover, specifically the inhibition of activation of bone resorption (Al Nofal et al. 2015; Naylor and Eastell 2012; Jung and Lein 2014). Collection of follow-up data is important for characterizing the safety and efficacy of neridronic acid. Subjects who receive any treatment, even a partial infusion, should be encouraged to remain in the trial for the full duration for follow-up safety and efficacy assessments.

Under certain situations, discontinuation from the trial may be required or be in the best interest of the subject from a risk/benefit perspective. [Table 1](#) lists mandatory and optional reasons for discontinuation from the trial.

Table 1: Reasons for compulsory and optional discontinuation of subjects

Reason	Discontinuation from trial	
	Compulsory	Optional
Enrollment failure (i.e., subject was not allocated to treatment due to failure to meet inclusion or exclusion criteria and did not receive IMP).	X	
Subject withdrawal of consent (the reason for withdrawal must be specified).	X	
Subject death.	X	
Subject loss to follow-up (i.e., no further contact with the subject is possible).	X	
Sponsor decision to discontinue the subject.	X	
Technical reasons (e.g., site is no longer able to function or participate in the trial, and the subject is too remote from other site locations).		X
Sponsor decision to terminate the trial.	X	
Other reasons (e.g., subject becomes engaged in litigation related to their disability from CRPS in which monetary gain may affect their objective participation in the trial).		X

CRPS = complex regional pain syndrome, IMP = investigational medicinal product.

9.3.2 Subject discontinuation from the IMP

Discontinuation of IMP applies only to Treatment Period A or Treatment Period B. Subjects who are discontinued from IMP should not be discontinued from the trial except for reasons indicated in [Table 1](#). Subjects who are discontinued from IMP should be encouraged to remain in the trial for their own safety and for the integrity of the trial.

Subjects must be evaluated prior to each infusion of IMP. The investigator must permanently or temporarily discontinue treatment with IMP for any reasons listed in [Table 2](#). The investigator may decide to temporarily discontinue a subject from receiving IMP for other reasons (e.g., if further assessments may be helpful to assure safety of the subject). The investigator may also choose to permanently discontinue a subject from treatment if they believe that continued exposure of the subject to neridronic acid may pose an undue risk to the subject, e.g., due to particular adverse events or due to deterioration in the subject's health for reasons related or unrelated to the treatment.

In situations where treatment is temporarily discontinued, Treatment Period A or Treatment Period B may be extended to a maximum of 21 days (for details, see footnote b) in [Section 1.7.1](#) and [Section 1.7.2](#)).

Table 2: Reasons for permanent and temporary discontinuation of subjects from IMP

Reason	Discontinuation from IMP	
	Permanent	Temporary
Symptomatic hypocalcemia.	X	
Serum calcium <7.8 mg/dL (<1.95 mmol/L). The subject may resume treatment following investigator assessment and a repeat serum calcium value above this limit (albumin-corrected serum calcium should be considered if serum albumin is below 3.5 g/dL).		X
Clinical signs of dehydration (e.g., dizziness, palpitations, confusion).		X
Test results suggestive of a possible change in renal function:		
<ul style="list-style-type: none"> A persistent ∇25% decrease in the eGFR from the last value observed prior to the first IMP administration, based on repeated central laboratory results from blood samples obtained at least 1 week apart ^a. 	X	
<ul style="list-style-type: none"> A ∇25% decrease in the eGFR from the last value observed prior to the first IMP administration. If a repeated measurement of eGFR is within 75% or more of the respective value, the subject may resume treatment ^a. 		X
<ul style="list-style-type: none"> A persistent urinary ACR based on an initial value >300 mg/g (semi-quantitative dipstick or quantitative urinary albumin and creatinine data from the central laboratory) and on a second value \geq150 mg/g (quantitative urinary albumin and creatinine data from the central laboratory) from urine samples obtained at least 1 week apart. 	X	
<ul style="list-style-type: none"> A urinary ACR >300 mg/g based on the results of the semi-quantitative dipstick or quantitative data from the central laboratory. The subject may resume treatment if quantitative urinary albumin and creatinine data from the central laboratory indicate a urinary ACR value <150 mg/g from urine samples obtained at least 1 week apart. 		X
<ul style="list-style-type: none"> A persistent eGFR <30 mL/min/1.73 m² based on repeated quantitative data from the central laboratory, with urine samples obtained at least 1 week apart. 	X	
<ul style="list-style-type: none"> An eGFR <30 mL/min/1.73 m². If a repeated measurement of eGFR is ∇30 mL/min/1.73 m², the subject may resume treatment. 		X
An average QTcF interval of >500 ms based on triplicate ECGs, or average QTcF interval of >480 ms with a concurrent increase in average QTcF interval >60 ms relative to the average of triplicate ECGs obtained at Visit 1.	X	
Pregnancy.	X	
Development of hypersensitivity to the IMP.	X	
Signs or symptoms of ocular inflammation: ^b		

Reason	Discontinuation from IMP	
	Permanent	Temporary
• Resolution of signs and symptoms within 5 days.		X
• Persistent or recurrent signs and symptoms.	X	
Newly occurring risk factors for osteonecrosis of the jaw (e.g., need for emergency dental surgery).	X	
Any other adverse event causing a significant deterioration in subject's health.		X
Major protocol deviations (e.g., serious non-compliance with protocol procedures, unsafe use of forbidden medication, abuse of illicit drugs, or other reckless behavior during the trial that may jeopardize the subject's safety or safety of other subjects or site staff).	X	

a) Not applicable if no eGFR value after first IMP administration is available. For both treatment periods, the last value observed prior to first IMP application in Treatment Period A will be used for calculating the decrease in eGFR.

b) Subjects should be assessed for ocular inflammation by the investigator prior to each infusion (signs and symptoms include eye redness and irritation, blurred vision, eye pain, and sensitivity to light). Subjects with signs or symptoms of ocular inflammation should be temporarily suspended from treatment. Subjects with resolution of signs and symptoms within 5 days may resume treatment. Subjects with persistent or recurrent signs and symptoms of ocular inflammation must be discontinued from IMP and undergo an ophthalmologic examination.

ACR = albumin to creatinine ratio, eGFR = estimated glomerular filtration rate, ECG = electrocardiogram, IMP = investigational medicinal product, QTcF = corrected QT interval (according to Fridericia's formula).

9.3.3 Procedure for the handling of discontinued subjects

9.3.3.1 Handling of subjects who discontinued from the trial

The principal investigator must document any discontinuation of a subject and inform the sponsor. Where applicable, the relevant IECs or IRBs must be informed with a detailed written explanation.

The following must be done for **all** discontinued subjects, including those who withdrew informed consent:

- Document the main reason for discontinuation from the trial.
- Ensure that all data collected until the time of discontinuation is transferred to the eCRF.
- Complete any other trial-related formalities, e.g., those related to discharge from the trial site.
- For subjects withdrawing consent, document in the source data the date and time of withdrawal.
- If possible, perform an Early Termination Visit, with procedures identical to Visit 17. Subjects who withdraw consent and agree to perform the Early Termination Visit must document their approval in writing.

9.3.3.2 Handling of subjects discontinued from the IMP but not from the trial

Subjects who are temporarily suspended from IMP may undergo abbreviated visits for safety assessments to support a decision to continue treatment or permanently discontinue IMP. Subjects

who are permanently discontinued from IMP should proceed to Visit 6 (for Treatment Period A) or Visit 15 (for Treatment Period B) at approximately 4 days after the last infusion, if possible; Visit 7 or Visit 16, respectively, and subsequent visits will proceed according to the original visit schedule (relative to Visit 2).

9.3.3.3 Replacement of subjects

Subjects will not be replaced.

9.3.4 Premature termination or suspension of the trial

The following criteria for premature termination or suspension of the trial apply:

- Significant changes in the risk-benefit profile assessment, based on emerging safety or efficacy information, such that continuation of the trial would compromise ethical treatment of subjects within or outside of the trial.
- Request for termination or suspension of the trial by the FDA or other regulatory agency.
- Decision by the sponsor to terminate the program.

The sponsor also reserves the right to close an investigational site, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for early closure of an investigational site include failure of the investigator to comply with the protocol, sponsor's procedures, or GCP guidelines; inadequate recruitment of subjects by the investigator; and enrollment target reached.

The relevant IECs or IRBs, the regulatory authorities, or the sponsor or the sponsor's authorized delegate alone or in conjunction have the power to make a binding decision to prematurely terminate or suspend the trial at any or all trial sites. In addition, for an individual trial site, this decision can be made by the principal investigator.

The party prematurely terminating or suspending the trial must promptly inform all other parties (i.e., the principal investigators, the relevant IECs or IRBs, the relevant regulatory authorities, or the sponsor/the sponsor's authorized delegate, as applicable).

In addition, if the principal investigator decides to terminate or suspend the trial at the trial site, they must promptly inform the subjects, ensure appropriate follow-up for any enrolled subjects, and provide the relevant IECs or IRBs and the sponsor or the sponsor's authorized delegate, as applicable, with a written explanation of the termination or suspension.

The international coordinating investigator and country-specific coordinating investigators must be informed immediately if the trial is prematurely terminated or suspended.

10 TRIAL TREATMENTS

10.1 Investigational medicinal products

10.1.1 Identity and composition – neridronic acid

Name:	Sodium neridronate hemi hydrate for intravenous infusion.
Active component:	Neridronic acid.
Dose (strength):	Sodium neridronate hemi hydrate 108 mg for intravenous infusion (equivalent to 100 mg neridronic acid) supplied in 8 mL of excipients.
Supplier:	Grünenthal GmbH, Aachen, Germany.

10.1.2 Identity and composition – matching placebo

Name:	Placebo matching sodium neridronate hemi hydrate for intravenous infusion.
Active component:	Not applicable.
Dose (strength):	Not applicable.
Supplier:	Grünenthal GmbH, Aachen, Germany.

For further information about the identity and composition of the IMPs, see the investigator's brochure and the clinical supply specification (available on request).

10.1.3 Preparation

The IMP is supplied in glass vials, each containing 108 mg sodium neridronate hemi hydrate (equivalent to 100 mg neridronic acid) or matching placebo in a total volume of 8 mL.

Instructions will be provided for the proper handling of vials.

The IMP will be prepared and infused by appropriately trained personnel at the trial sites.

For each infusion, before use, the IMP must be diluted in sterile normal saline (0.9% NaCl, e.g., United States Pharmacopeia (USP) grade saline for injection) to a volume of approximately 500 mL. For subjects with moderate renal impairment, the respective reduced volume of IMP will be used (see Section 10.2). The IMP should not be diluted in solutions containing calcium and should not be infused in combination with any other medication. The volume of IMP transferred to the infusion bag must be recorded in the eCRF.

10.1.4 Packaging and labeling

For detailed information about the packaging and labeling, see the clinical supply specification (available on request).

10.1.5 Delivery, storage, and disposal

For detailed information about the distribution of the IMP, see the clinical distribution specification (available on request).

At the investigator's site, the IMPs must be stored in a secure and temperature controlled room with restricted access and temperature monitoring and must not be stored above 30°C.

The medication must not be frozen or refrigerated in order to maintain the quality of the packaging and labeling.

Controls will be implemented at the trial site to ensure documented compliance with these requirements.

10.2 Administration of investigational medicinal products

For subjects with no or mild renal impairment, the full contents of a single vial (8 mL) will be diluted in 500 mL normal saline and administered by slow intravenous infusion (240 minutes [maximum 260 minutes]) at Visit 2, Visit 3, Visit 4, and Visit 5, resulting in a total dose of 400 mg neridronic acid or matching placebo. The complete solution volume of 500 mL should be administered at each infusion visit unless treatment is suspended for safety reasons. Any administration of less than 500 mL should be noted and recorded in the eCRF. No more than 4 infusions (400 mg total dose) may be administered to any subject in Treatment Period A.

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

A maximum total dose of neridronic acid 800 mg is planned for subjects allocated to neridronic acid in Treatment Period A who go on to complete Treatment Period B.

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

CKD-EPI Stage 3a (eGFR 45 mL/min/1.73 m² to <60 mL/min/1.73 m²)

6 mL of solution from a single vial (corresponding to neridronic acid 75 mg) will be 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 m² to <45 mL/min/1.73 m²)

5 mL of solution from a single vial (corresponding to neridronic acid 62.5 mg) will be 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.

Any decision regarding dose adjustment will be based on the last eGFR value available before Visit 2 for Treatment Period A and the last eGFR value available before Visit 11 for Treatment Period B.

All infusions must be performed at the trial site under the supervision of medical staff.

Subjects must be assessed for hydration status prior to each infusion to minimize risk for renal toxicity. Hydration status will be evaluated by querying subjects about risk factors for volume

depletion (poor oral fluid intake, diarrhea) and examining vital signs, mucous membranes, and sensorium. Oral fluid intake may be sufficient for correction of mild dehydration.

The IMP discontinuation criteria described in Section 9.3.2 must be evaluated prior to each infusion. The 10-day Treatment Period A (or Treatment Period B) may be extended in the event of temporary discontinuation of IMP, as described in Section 9.3.2.

The infusion site will be selected to avoid inducing pain in the CRPS-affected limb.

10.3 Method of assigning subjects to treatment (allocation)

On Day 1, subjects who comply with all inclusion criteria and do not meet any of the exclusion criteria will be randomly allocated to 1 of the 2 treatment groups in a 1:1 ratio stratified by geographic region. Treatment assignment will be performed centrally using an interactive response technology system prior to the first intravenous infusion of IMP. The details of the vendor and system will be filed in the trial master file.

The investigator (or delegate) must log into the system using their own user identification number and a password. The investigator (or delegate) will enter the subject's number and other information required by the system to obtain a medication number. The medication number will then be used to select the correct package of IMP to give to the subject.

10.4 Blinding and unblinding

10.4.1 Methods of blinding

The subject's initial treatment will be blinded until the 26-week analysis. However, investigators and subjects will not be informed about the initial treatment allocation at any time before database lock of the full trial.

Randomization and blinding will be performed in accordance with the sponsor's standard operating procedures (SOPs).

10.4.2 Methods of unblinding

All persons involved in the conduct, data management, and analysis of the trial will remain blinded until unblinding is performed after database lock at the 26-week analysis. Except as indicated below for reasons of subject safety, no subject is to be unblinded until the complete dataset has been entered into the database and the database has been locked.

Personnel in the sponsor's departments of clinical trial supply and pharmacokinetics as well as the bioanalytical laboratory will be unblinded according to the sponsor's SOPs.

10.4.3 Identification of IMPs in emergency situations

The investigator and the responsible drug safety department of the sponsor will receive appropriate methods for unblinding of single cases, i.e., interactive response technology system access to unblinding functionality.

The code may be broken when it is necessary and in that subject's interest in order to identify the IMPs given, e.g., if knowing the identification of the treatment arm would lead to the investigator treating the subject differently. In addition, within drug safety, the code may be broken for

regulatory reporting, medico-scientific assessment of adverse events, or on request of the qualified person for pharmacovigilance.

For every subject whose blind was broken, the following information must be documented on an “unblinding an individual subject form”:

- The reason for, the date, and time of unblinding.
- The person(s) informed of the treatment allocation must be identified.

In order to maintain the double-blind nature of the trial, the allocation of IMPs for the subject must not be communicated further unless required for the surveillance of the subject or if necessary for urgent risk to benefit re-evaluation and/or measures for urgent risk minimization.

If required by local regulations, it may be that the IEC, IRB, or the international coordinating investigator needs to be informed.

10.5 Allowed and forbidden prior/concomitant medications or therapies

Information on allowed or forbidden prior/concomitant medications or therapies is provided in Section 1.4.2.

For the purposes of data reporting by the site, the cutoff for reporting medication as either prior or concomitant is defined as the start of the first administration of IMP.

The allowed and forbidden concomitant medications or therapies will be explained to the subject by the investigator.

In emergency situations, subjects should be treated according to standard medical practice (see Section 11.3.1).

For information about potential drug-drug interactions, see Section 7.3.4.1 of the neridronic acid investigator’s brochure.

10.6 Documentation of drug accountability

The principal investigator must ensure that documentation is maintained for the receipt, inventory, use, and destruction or return of unused, used, or partially used packages of IMPs. The documentation must include IMP name, dates, quantities, subject numbers, batch/serial numbers or other identification numbers, expiration dates, and the means to identify the subject to whom it was given.

Documentation must be maintained for the checking of drug accountability.

Before the unused IMPs supplied to the trial site are returned or destroyed, the principal investigator must allow sponsor representatives to perform drug reconciliation. The entries in the documentation will be compared with the returned and residual IMPs and the administration/intake as documented in the eCRF, with clarification of any discrepancies or inconsistencies.

11 COURSE OF THE TRIAL AND CONDITIONS

See Section 1.1.1 for a flow diagram summary of the trial and Section 1.7 for tabular schedules of events.

11.1 Course of the trial

Blood samples for bone turnover markers should be collected in the morning under fasted conditions at Visits 2, 6, 7, 8, 10, 15, 16, and 17. Therefore, these visits should be attended in a fasting state (at least 8 hours).

The site should remind the subject 2 days before the scheduled visits that they should come to the site in a fasted state at these visits.

Fasting, non-fasting, or insufficient fasting should be documented at these visits. Non-fasting or insufficient fasting will not be documented as a protocol deviation (see Section 3.2).

11.1.1 Enrollment Period

The Enrollment Period consists of an Enrollment Visit (Visit 1) from Day -60 to Day -8 and a baseline pain assessment phase from Day -7 to Day -1 during which subjects will record pain intensity ratings in the electronic diary. These pain intensity ratings will be used to calculate the baseline average pain intensity score.

Additional visits are allowed during the Enrollment Period to confirm normalization of laboratory values (e.g., for subjects with vitamin D deficiency, up to a maximum of 4 times repeated laboratory testing for vitamin D in 60 days). For details of repeat testing, see Section 1.3.2.

11.1.1.1 Visit 1 (Day -60 to Day -8)

The following evaluations will be performed:

- Obtain written informed consent (the specific informed consent form for pharmacogenetic and omics sampling should preferably be signed at Visit 1, but has to be signed at the latest at Visit 2 before the sample is taken).
- Record demographic data (date of signing the informed consent form, sex, race/ethnicity, age, height, and body mass index [automatically calculated in the eCRF]).
- Record medical history.
- Record CRPS history (for details, see Section 12.2.3.1).
- Record dental history (for details, see Section 12.2.3.2).
- Record physical examination outcome.
- Record body weight.
- Record vital signs.
- Record triplicate 12-lead ECG.
- Record prior/concomitant medications and therapies (dose and dosing frequency data must be recorded).
- Record adverse events.

- Take blood for safety laboratory testing.
- Collect urine for quantitative urinalysis at the central laboratory.
- Perform dipstick urinalysis.
- Perform a urine β -HCG pregnancy test.
- Perform urine drugs of abuse testing.
- Complete the assessment of the signs and symptoms of CRPS (for details, see Section 12.3.6).
- Dispense subject trial card.
- Dispense calcium and vitamin D supplements.
- Review inclusion/exclusion criteria.
- Dispense electronic diary.
- Training for electronic diary.

11.1.1.2 Baseline pain assessment phase (Day -7 to Day -1)

In order to calculate the baseline pain intensity score, subjects will be asked to rate their average CRPS-related pain intensity using an 11-point NRS once daily (in the evening) during the last 7 days prior to Visit 2, in the electronic diary. Subjects will also be asked to rate their worst and their current CRPS-related pain intensity once daily during the same period of time. The worst and average pain will be based on a 24-hour recall period.

11.1.2 Treatment Period A

Infusion visits should be separated by 3-day intervals to the extent possible (i.e., Day 1, Day 4, Day 7, and Day 10). Infusion visits on consecutive days are not allowed. The full dosing period must not exceed 21 days from the first infusion (Visit 2). To facilitate scheduling, the interval between infusion visits may be adapted, provided the 21 day time period is not exceeded and discontinuation criteria can be assessed. In case of suspension of treatment due to a suspected safety concern or a visit scheduling difficulty, resumption of treatment is allowed upon resolution of findings, with sponsor agreement.

11.1.2.1 Visit 2 (Day 1)

The following evaluations will be performed prior to the start of IMP infusion:

- Record physical examination outcome (change from Visit 1).
- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes prior to the start of infusion).
- Record adverse events.
- Take blood for safety laboratory testing.
- Collect urine for quantitative urinalysis at the central laboratory.
- Perform dipstick urinalysis.
- Perform semi-quantitative dipstick urinalysis for urinary ACR.
- Perform a urine β -HCG pregnancy test.

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- Perform urine drugs of abuse testing.
 - Complete the assessment of the signs and symptoms of CRPS (for details, see Section 12.3.6).
 - Review inclusion/exclusion criteria.
 - Compliance assessment for electronic diary.
 - Check trial discontinuation criteria (for details, see Section 9.3.1).
 - Check IMP suspension criteria (for details, see Section 9.3.2).
 - Ask the subject to complete the EQ-5D-5L.
 - Ask the subject to record the average, worst, and current pain on the tablet computer at the site.
 - Measure edema, DMA, PPT, and AROM.
 - Ask the subject to complete the PROMIS-29 profile and the PROMIS-EDDEP39 (the investigator should review the subject's answer to the PROMIS EDDEP39 question before the subject leaves the site and in case of suicidal ideation the investigator should consider involvement of a mental health professional).
 - Ask the subject to complete the 6 neuropathic pain items of the SF-MPQ-2.
 - Ask the subject to complete the PCS.
 - Ask the subject to complete the PSEQ.
 - Ask the subject to complete the PGI-S.
 - Ask the subject to complete the WPAI: CRPS (US sites only).
 - Collect information for medical resources utilization and health economics (US sites only).
 - Take blood for pharmacokinetic evaluation (see Section 1.7.1 for time point).
 - Take blood for bone turnover marker evaluation.
 - Take blood for sIL-2R testing.
 - Take blood for pharmacogenetic and omics testing (see Section 11.1.1.1 for details of obtaining informed consent).

Compliance with inclusion and exclusion criteria must be confirmed before allocation to IMP. The baseline average pain intensity score must be confirmed prior to allocation by checking the electronic diary, which will provide an automatic calculation. A baseline average pain intensity score of at least 4 on the 11-point NRS is required.

A subject who has not met average baseline pain intensity requirements due to lack of compliance with the electronic diary (at least 4 average pain intensity ratings) may be rescheduled for Visit 2 (allowed only once), with appropriate re-training to ensure compliance with use of the electronic diary. Subjects who do not meet eligibility criteria due to an inadequate average pain level (less than 4 on the NRS) will be excluded from the trial.

Once the above evaluations have been performed, the subject will be allocated to IMP using the interactive response technology system and the IMP will be administered (for details, see Section 10.2).

During the infusion, a blood sample will be taken for pharmacokinetic evaluation (see Section 1.7.1 for time point).

The following evaluations will be performed after the infusion:

- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes after the infusion).
- Record prior/concomitant medications and therapies.
- Record adverse events.
- Take blood for pharmacokinetic evaluation (see Section 1.7.1 for time point).

11.1.2.2 Visit 3 (Day 4; ±1 day)

The following evaluations will be performed prior to the start of IMP infusion:

- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes prior to the start of infusion).
- Record adverse events.
- Take blood for safety laboratory testing.
- Collect urine for quantitative urinalysis at the central laboratory.
- Perform dipstick urinalysis.
- Perform semi-quantitative dipstick urinalysis for urinary ACR.
- Perform a urine β -HCG pregnancy test.
- Compliance assessment for electronic diary.
- Check trial discontinuation criteria (for details, see Section 9.3.1).
- Check IMP suspension criteria (for details, see Section 9.3.2).
- Take blood for pharmacokinetic evaluation (see Section 1.7.1 for time point).

Once the above evaluations have been performed, the IMP will be administered (for details, see Section 10.2).

The following evaluations will be performed after the infusion:

- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes after the infusion).
- Record concomitant medications and therapies.
- Record adverse events.
- Take blood for pharmacokinetic evaluation (see Section 1.7.1 for time point).

11.1.2.3 Visit 4 (Day 7; ±1 day)

The following evaluations will be performed prior to the start of IMP infusion:

- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes prior to the start of infusion).
- Record adverse events.

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- Take blood for safety laboratory testing.
 - Collect urine for quantitative urinalysis at the central laboratory.
 - Perform dipstick urinalysis.
 - Perform semi-quantitative dipstick urinalysis for urinary ACR.
 - Perform a urine β -HCG pregnancy test.
 - Compliance assessment for electronic diary.
 - Check trial discontinuation criteria (for details, see Section 9.3.1).
 - Check IMP suspension criteria (for details, see Section 9.3.2).
 - Take blood for pharmacokinetic evaluation (see Section 1.7.1 for time point).

Once the above evaluations have been performed, the IMP will be administered (for details, see Section 10.2).

The following evaluations will be performed after the infusion:

- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes after the infusion).
- Record concomitant medications and therapies.
- Record adverse events.
- Take blood for pharmacokinetic evaluation (see Section 1.7.1 for time point).

11.1.2.4 Visit 5 (Day 10; ± 1 day)

The following evaluations will be performed prior to the start of IMP infusion:

- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes prior to the start of infusion).
- Record adverse events.
- Take blood for safety laboratory testing.
- Collect urine for quantitative urinalysis at the central laboratory.
- Perform dipstick urinalysis.
- Perform semi-quantitative dipstick urinalysis for urinary ACR.
- Perform a urine β -HCG pregnancy test.
- Compliance assessment for electronic diary.
- Check trial discontinuation criteria (for details, see Section 9.3.1).
- Check IMP suspension criteria (for details, see Section 9.3.2).
- Take blood for pharmacokinetic evaluation (see Section 1.7.1 for time point).

Once the above evaluations have been performed, the IMP will be administered (for details, see Section 10.2).

During the infusion, a blood sample will be taken for pharmacokinetic evaluation (see Section 1.7.1 for time point).

The following evaluations will be performed after the infusion:

- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes after the infusion).
- Record concomitant medications and therapies.
- Record adverse events.
- Take blood for pharmacokinetic evaluation (see Section 1.7.1 for time point).

11.1.3 Follow-up Period 1

In case of interruption or suspension of treatment, the first follow-up visit (Visit 6) should be scheduled at 4 days (± 2 days) after the last infusion visit. All subsequent visits must remain as originally scheduled relative to Visit 2 (e.g., Visit 7 occurs at 42 days [6 weeks] ± 3 days after Visit 2). No more than 4 infusions are allowed in Treatment Period A; any partial infusion (exceeding 20 mL) must be counted as 1 infusion.

11.1.3.1 Visit 6 (Day 15 [Week 2]; ± 2 days)

The following evaluations will be performed:

- Record vital signs.
- Record concomitant medications and therapies.
- Record adverse events.
- Take blood for safety laboratory testing.
- Collect urine for quantitative urinalysis at the central laboratory.
- Perform dipstick urinalysis.
- Compliance assessment for electronic diary.
- Check trial discontinuation criteria.
- Take blood for pharmacokinetic evaluation (at any time point during the visit).
- Take blood for bone turnover marker evaluation.

11.1.3.2 Visit 7 (Day 43 [Week 6]; ± 3 days)

The following evaluations will be performed:

- Record vital signs.
- Record concomitant medications and therapies.
- Record adverse events.
- Take blood for safety laboratory testing.
- Collect urine for quantitative urinalysis at the central laboratory.
- Perform dipstick urinalysis.
- Complete the assessment of the signs and symptoms of CRPS (for details, see Section 12.3.6).
- Compliance assessment for electronic diary.
- Check trial discontinuation criteria.

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- Ask the subject to record the average, worst, and current pain on the tablet computer at the site.
 - Measure edema, DMA, PPT, and AROM.
 - Ask the subject to complete the PROMIS-29 profile and the PROMIS-EDDEP39 (the investigator should review the subject's answer to the PROMIS EDDEP39 question before the subject leaves the site and in case of suicidal ideation the investigator should consider involvement of a mental health professional).
 - Ask the subject to complete the 6 neuropathic pain items of the SF-MPQ-2.
 - Ask the subject to complete the PCS.
 - Ask the subject to complete the PSEQ.
 - Ask the subject to complete the PGI-S.
 - Take blood for bone turnover marker evaluation.
 - Ask the subject to complete the PGIC.

11.1.3.3 Visit 8 (Day 85 [Week 12]; +7 days)

Visit 8 must not occur prior to Day 85 in order for the subjects to have complete electronic diary data through Week 12 for the calculation of the primary endpoint.

The following evaluations will be performed:

- Record physical examination outcome (change from Visit 2).
- Record vital signs.
- Record concomitant medications and therapies.
- Record adverse events.
- Take blood for safety laboratory testing.
- Collect urine for quantitative urinalysis at the central laboratory.
- Perform dipstick urinalysis.
- Complete the assessment of the signs and symptoms of CRPS (for details, see Section 12.3.6).
- Training on electronic diary as, from Week 12, the electronic diary will ask for weekly assessments of pain intensity.
- Compliance assessment for electronic diary.
- Check trial discontinuation criteria.
- Ask the subject to record the average, worst, and current pain on the tablet computer at the site.
- Measure edema, DMA, PPT, and AROM.
- Ask the subject to complete the EQ-5D-5L.
- Ask the subject to complete the PROMIS-29 profile and the PROMIS-EDDEP39 (the investigator should review the subject's answer to the PROMIS EDDEP39 question before the subject leaves the site and in case of suicidal ideation the investigator should consider involvement of a mental health professional).

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- Ask the subject to complete the 6 neuropathic pain items of the SF-MPQ-2.
 - Ask the subject to complete the PCS.
 - Ask the subject to complete the PSEQ.
 - Ask the subject to complete the PGI-S.
 - Ask the subject to complete the WPAI: CRPS (US sites only).
 - Collect information for medical resources utilization and health economics (US sites only).
 - Take blood for bone turnover marker evaluation.
 - Take blood for sIL-2R testing.
 - Take blood for omics testing.
 - Ask the subject to complete the PGIC.

11.1.3.4 Visit 9 (Day 113 [Week 16]; ±4 days)

The following evaluations will be performed:

- Record vital signs.
- Record concomitant medications and therapies.
- Record adverse events.
- Complete the assessment of the signs and symptoms of CRPS (for details, see Section 12.3.6).
- Compliance assessment for electronic diary.
- Check trial discontinuation criteria.
- Ask the subject to record the average, worst, and current pain on the tablet computer at the site.
- Ask the subject to complete the pain intensity question (question number 29, GLOBAL07) of the PROMIS-29 profile.
- Ask the subject to complete the PGI-S.
- Ask the subject to complete the PGIC.

11.1.3.5 Visit 10 (Day 155 [Week 22]; ±4 days)

The following evaluations will be performed:

- Record vital signs.
- Record triplicate 12-lead ECG.
- Record concomitant medications and therapies.
- Record adverse events.
- Take blood for safety laboratory testing.
- Collect urine for quantitative urinalysis at the central laboratory.
- Perform dipstick urinalysis.
- Perform a urine β -HCG pregnancy test.

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- Complete the assessment of the signs and symptoms of CRPS (for details, see Section 12.3.6).
 - Compliance assessment for electronic diary.
 - Check trial discontinuation criteria.
 - Ask the subject to record the average, worst, and current pain on the tablet computer at the site.
 - Ask the subject to complete the pain intensity question (question number 29, GLOBAL07) of the PROMIS-29 profile.
 - Ask the subject to complete the PGI-S.
 - Take blood for bone turnover marker evaluation.
 - Ask the subject to complete the PGIC.

11.1.4 Follow-up Period 2

11.1.4.1 Visit 11 (Day 183 [Week 26]; +7 days)

Visit 11 must not occur prior to Day 183, to ensure a full 6 months of follow-up for all subjects.

If Visit 11 is not performed on Day 183, Visit 12 to Visit 15 should proceed in accordance with the originally scheduled time windows relative to Visit 11.

The following evaluations will be performed for all subjects:

- Record physical examination outcome (change from Visit 8).
- Record body weight.
- Record vital signs.
- Record concomitant medications and therapies.
- Assess further need of concomitant treatment for CRPS (in particular opioids), including decreases in dose or frequency as applicable.
- Record adverse events.
- Take blood for safety laboratory testing.
- Collect urine for quantitative urinalysis at the central laboratory.
- Perform dipstick urinalysis.
- Compliance assessment for electronic diary.
- Check trial discontinuation criteria (for details, see Section 9.3.1).
- Ask the subject to record the average, worst, and current pain on the tablet computer at the site.
- Measure edema, DMA, PPT, and AROM.
- Ask the subject to complete the EQ-5D-5L.
- Ask the subject to complete the PROMIS-29 profile and the PROMIS-EDDEP39 (the investigator should review the subject's answer to the PROMIS EDDEP39 question before the subject leaves the site and in case of suicidal ideation the investigator should consider involvement of a mental health professional).

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- Ask the subject to complete the 6 neuropathic questions of the SF-MPQ-2.
 - Ask the subject to complete the PCS.
 - Ask the subject to complete the PSEQ.
 - Ask the subject to complete the PGI-S.
 - Ask the subject to complete the WPAI: CRPS (US sites only).
 - Collect information for medical resources utilization and health economics (US sites only).
 - Take blood for sIL-2R testing.
 - Take blood for omics testing.
 - Ask the subject to complete the PGIC.
 - Check the criteria to continue into Treatment Period B.

Decision to go into Treatment Period B

Compliance with the criteria to continue into Treatment Period B must be confirmed before allocation to IMP. The pain intensity question (question number 29, GLOBAL07) of the PROMIS-29 profile has to have a value of at least 4 at Visit 11. Subjects who do not meet the criteria to continue into Treatment Period B will continue with the Follow-up Period 2.

11.1.4.1.1 Subjects meeting the criteria to continue into Treatment Period B

For subjects continuing into Treatment Period B, the following evaluations will be performed prior to the start of IMP infusion:

- Record triplicate 12-lead ECG (at least 15 minutes prior to the start of infusion).
- Perform semi-quantitative dipstick urinalysis for urinary ACR.
- Perform a urine β -HCG pregnancy test.
- Perform urine drugs of abuse testing.
- Complete the assessment of the signs and symptoms of CRPS (for details, see Section 12.3.6).
- Check IMP suspension criteria (for details, see Section 9.3.2).
- Take blood for pharmacokinetic evaluation (see Section 1.7.2 for time point).

Once the above evaluations have been performed, the subject will be re-allocated to IMP using the interactive response technology system and the IMP will be administered (for details, see Section 10.2).

During the infusion, a blood sample will be taken for pharmacokinetic evaluation (see Section 1.7.2 for time point).

The following evaluations will be performed after the infusion:

- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes after the infusion).
- Record adverse events.
- Take blood for pharmacokinetic evaluation (see Section 1.7.2 for time point).

11.1.4.2 Treatment Period B

Infusion visits should be separated by 3-day intervals to the extent possible (i.e., Day 183, Day 186, Day 189, and Day 192). Infusion visits on consecutive days are not allowed. The full dosing period must not exceed 21 days from the first infusion of Treatment Period B (Visit 11). To facilitate scheduling, the interval between infusion visits may be adapted, provided the 21 day time period is not exceeded and discontinuation criteria can be assessed. In case of suspension of treatment due to a suspected safety concern or a visit scheduling difficulty, resumption of treatment is allowed upon resolution of findings, with sponsor agreement. In case of interruption or suspension of treatment, the first follow-up visit (Visit 15) should be scheduled at 4 days (± 2 days) after the last infusion visit of Treatment Period B. All subsequent visits must remain as originally scheduled relative to Visit 11. No more than 4 infusions are allowed in Treatment Period B; any partial infusion (exceeding 20 mL) must be counted as 1 infusion.

11.1.4.2.1 Visit 12 (Day 186; ± 1 day) - only subjects receiving a second treatment course

The following evaluations will be performed prior to the start of IMP infusion:

- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes prior to the start of infusion).
- Record adverse events.
- Take blood for safety laboratory testing.
- Collect urine for quantitative urinalysis at the central laboratory.
- Perform dipstick urinalysis.
- Perform semi-quantitative dipstick urinalysis for urinary ACR.
- Perform a urine β -HCG pregnancy test.
- Compliance assessment for electronic diary.
- Check trial discontinuation criteria (for details, see Section 9.3.1).
- Check IMP suspension criteria (for details, see Section 9.3.2).
- Take blood for pharmacokinetic evaluation (see Section 1.7.2 for time point).
- Ask the subject to record the average, worst, and current pain on the tablet computer at the site.

Once the above evaluations have been performed, the IMP will be administered (for details, see Section 10.2).

The following evaluations will be performed after the infusion:

- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes after the infusion).
- Record concomitant medications and therapies.
- Record adverse events.
- Take blood for pharmacokinetic evaluation (see Section 1.7.2 for time point).

11.1.4.2.2 Visit 13 (Day 189; ±1 day) - only subjects receiving a second treatment course

The following evaluations will be performed prior to the start of IMP infusion:

- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes prior to the start of infusion).
- Record adverse events.
- Take blood for safety laboratory testing.
- Collect urine for quantitative urinalysis at the central laboratory.
- Perform dipstick urinalysis.
- Perform semi-quantitative dipstick urinalysis for urinary ACR.
- Perform a urine β -HCG pregnancy test.
- Compliance assessment for electronic diary.
- Check trial discontinuation criteria (for details, see Section 9.3.1).
- Check IMP suspension criteria (for details, see Section 9.3.2).
- Take blood for pharmacokinetic evaluation (see Section 1.7.2 for time point).
- Ask the subject to record the average, worst, and current pain on the tablet computer at the site.

Once the above evaluations have been performed, the IMP will be administered (for details, see Section 10.2).

The following evaluations will be performed after the infusion:

- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes after the infusion).
- Record concomitant medications and therapies.
- Record adverse events.
- Take blood for pharmacokinetic evaluation (see Section 1.7.2 for time point).

11.1.4.2.3 Visit 14 (Day 192; ±1 day) - only subjects receiving a second treatment course

The following evaluations will be performed prior to the start of IMP infusion:

- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes prior to the start of infusion).
- Record adverse events.
- Take blood for safety laboratory testing.
- Collect urine for quantitative urinalysis at the central laboratory.
- Perform dipstick urinalysis.
- Perform semi-quantitative dipstick urinalysis for urinary ACR.
- Perform a urine β -HCG pregnancy test.
- Compliance assessment for electronic diary.
- Check trial discontinuation criteria (for details, see Section 9.3.1).

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- Check IMP suspension criteria (for details, see Section 9.3.2).
 - Take blood for pharmacokinetic evaluation (see Section 1.7.2 for time point).
 - Ask the subject to record the average, worst, and current pain on the tablet computer at the site.

Once the above evaluations have been performed, the IMP will be administered (for details, see Section 10.2).

During the infusion, a blood sample will be taken for pharmacokinetic evaluation (see Section 1.7.2 for time point).

The following evaluations will be performed after the infusion:

- Record vital signs.
- Record triplicate 12-lead ECG (at least 15 minutes after the infusion).
- Record concomitant medications and therapies.
- Record adverse events.
- Take blood for pharmacokinetic evaluation (see Section 1.7.2 for time point).

11.1.4.3 Visit 15 (Day 197 [Week 28]; +/-2 days) - only subjects receiving a second treatment course

The following evaluations will be performed:

- Record vital signs.
- Record triplicate 12-lead ECG.
- Record concomitant medications and therapies.
- Record adverse events.
- Take blood for safety laboratory testing.
- Collect urine for quantitative urinalysis at the central laboratory.
- Perform dipstick urinalysis.
- Compliance assessment for electronic diary.
- Check trial discontinuation criteria.
- Ask the subject to record the average, worst, and current pain on the tablet computer at the site.
- Ask the subject to complete the PROMIS-29 profile.
- Ask the subject to complete the 6 neuropathic questions of the SF-MPQ-2.
- Ask the subject to complete the PGI-S.
- Take blood for pharmacokinetic evaluation (at any time point during the visit).
- Take blood for bone turnover marker evaluation.
- Ask the subject to complete the PGIC.

11.1.4.4 Visit 16 (Day 253 [Week 36]; ±7 days) - for all subjects

The following evaluations will be performed:

- Record vital signs.
- Record concomitant medications and therapies.
- Assess further need of concomitant treatment for CRPS (in particular opioids), including decreases in dose or frequency as applicable.
- Record adverse events.
- Take blood for safety laboratory testing.
- Collect urine for quantitative urinalysis at the central laboratory.
- Perform dipstick urinalysis.
- Complete the assessment of the signs and symptoms of CRPS.
- Compliance assessment for electronic diary.
- Check trial discontinuation criteria.
- Ask the subject to record the average, worst, and current pain on the tablet computer at the site.
- Measure edema, DMA, PPT, and AROM.
- Ask the subject to complete the EQ-5D-5L.
- Ask the subject to complete the PROMIS-29 profile and the PROMIS-EDDEP39 (the investigator should review the subject's answer to the PROMIS EDDEP39 question before the subject leaves the site and in case of suicidal ideation the investigator should consider involvement of a mental health professional).
- Ask the subject to complete the 6 neuropathic questions of the SF-MPQ-2.
- Ask the subject to complete the PCS.
- Ask the subject to complete the PSEQ.
- Ask the subject to complete the PGI-S.
- Ask the subject to complete the WPAI: CRPS (US sites only).
- Collect information for medical resources utilization and health economics (US sites only).
- Take blood for bone turnover marker evaluation.
- Ask the subject to complete the PGIC.

11.1.4.5 Visit 17 (Day 365 [Week 52]; +7 days) - for all subjects

Visit 17 must not occur prior to Day 365, to ensure that the subjects are followed up for a full 12 months.

The following evaluations will be performed:

- Record physical examination outcome (change from Visit 11).
- Record body weight.
- Record vital signs.

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- Record triplicate 12-lead ECG.
 - Record concomitant medications and therapies.
 - Record adverse events.
 - Take blood for safety laboratory testing.
 - Collect urine for quantitative urinalysis at the central laboratory.
 - Perform dipstick urinalysis.
 - Perform a urine β -HCG pregnancy test.
 - Complete the assessment of the signs and symptoms of CRPS.
 - Compliance assessment for electronic diary.
 - Collect electronic diary.
 - Ask the subject to record the average, worst, and current pain on the tablet computer at the site.
 - Measure edema, DMA, PPT, and AROM.
 - Ask the subject to complete the EQ-5D-5L.
 - Ask the subject to complete the PROMIS-29 profile and the PROMIS-EDDEP39 (the investigator should review the subject's answer to the PROMIS EDDEP39 question before the subject leaves the site and in case of suicidal ideation the investigator should consider involvement of a mental health professional).
 - Ask the subject to complete the 6 neuropathic questions of the SF-MPQ-2.
 - Ask the subject to complete the PCS.
 - Ask the subject to complete the PSEQ.
 - Ask the subject to complete the PGI-S.
 - Ask the subject to complete the WPAI: CRPS (US sites only).
 - Collect information for medical resources utilization and health economics (US sites only).
 - Take blood for bone turnover marker evaluation.
 - Ask the subject to complete the PGIC.

11.2 Examination hierarchy and time windows

Pain evaluations and ECGs should be taken before invasive procedures. When practical, blood samples for safety laboratory and pharmacokinetic evaluation should be taken after all non-invasive procedures (including completion of questionnaires) have been finished.

11.3 Conditions during the trial

11.3.1 Medical care

Hospitalization of subjects for the entire treatment or certain trial periods, for logistical reasons, is allowed, if agreed by the sponsor prior to hospitalization for this reason.

For any adverse events, a causal or symptomatic treatment according to standard medical practice should be provided if deemed necessary by the investigator. The medical care given to, and medical decisions made on behalf of the subjects must be the responsibility of a qualified physician.

See the guidance in the investigator's brochure for precautions and the handling of emergencies.

11.3.2 Meals and fluid intake restrictions

Visits 2, 6, 7, 8, 10, 15, 16, and 17 should be attended in a fasting state (at least 8 hours).

Light meals are allowed after sampling for bone turnover markers and may be provided before, during, and/or after IMP infusions during Treatment Period A (Visit 2 to Visit 5) and Treatment Period B (Visit 11 to Visit 14).

Fluid intake is recommended prior to and during the infusions. Subjects must be well hydrated prior to the start of infusions.

11.3.3 Dental hygiene

Subjects should adhere to the following recommendations for good dental hygiene throughout the trial:

- Brush teeth twice a day (with a fluoride toothpaste).
- Floss regularly to remove plaque from between teeth.
- Continue with routine dental visits (as recommended by their dentist) for a check-up and professional cleaning.

Subjects will be advised to notify the investigator if they experience any dental pain or swelling of the gums, infection in the mouth, any pain related to use of dentures, or are planning dental work.

11.3.4 Counseling of women of reproductive age

All women, including those with tubal ligation, will be considered to be of child-bearing potential unless they have been postmenopausal for at least 2 years or have undergone a hysterectomy.

Trial subjects must use contraception as defined in inclusion criterion 6.

Women will be counseled to contact the investigator or site staff immediately if pregnancy is suspected.

11.4 Subject trial cards

Subjects who are enrolled in the trial will receive a subject trial card (the time of card distribution is given in Section 1.7.1 and Section 1.7.2). The trial card will list the following information:

- Name of the subject and a statement that he/she is currently participating in a clinical trial.
- Trial code.
- Dates of all individual visits.
- Name of the principal investigator for that trial site.
- Contact (telephone) number at the trial site.

11.5 Provisions of any additional care of subjects after trial termination

Subjects who complete or discontinue from the trial should continue treatment with their regular physicians in accordance with standard practices.

12 TRIAL ASSESSMENTS

12.1 Overview of blood sampling in this trial

The total blood volume drawn per subject during the trial is estimated to be approximately 314 mL for subjects included in Treatment Period B and approximately 230 mL for subjects not included in Treatment Period B (unless additional blood is required for repeated assessment due to an abnormal laboratory value, adverse event, or technical reason such as hemolysis of the blood sample).

Sampling times are given in the schedules of events (Section 1.7).

Table 3: Planned approximate blood sampling volumes collected from each subject

Test	Unit volume of blood	Number of samples	Total
Pharmacokinetic evaluation	4 mL	11	44 mL
Additional pharmacokinetic evaluation for subjects in Treatment Period B	4 mL	11	44 mL
Sampling for bone turnover markers	7.5 mL	7	52.5 mL
Additional sampling for bone turnover markers for subjects in Treatment Period B	7.5 mL	1	7.5 mL
Sampling for pharmacogenetic testing (optional)	5 mL	1	5 mL
Sampling for omics testing (optional)	5 mL	3	15 mL
Sampling for sIL-2R testing	5 mL	3	15 mL
Sampling for central safety laboratory testing:			
Hematology	3 mL	12	36 mL
Clinical chemistry	5 mL	12	60 mL
Parathyroid hormone	3 mL	1	3 mL
Additional sampling for central safety laboratory testing for subjects in Treatment Period B:			
Hematology	3 mL	4	12 mL
Clinical chemistry	5 mL	4	20 mL
Total for subjects included in Treatment Period B		70	314.0 mL
Total for subjects not included in Treatment Period B		50	230.5 mL

The volume of blood taken may be individually variable due to local practices and the potential need for resampling.

12.2 Collection of demographic data and other baseline characteristics

12.2.1 Demographic data

Demographic data to be collected and recorded for this trial include date of signing the informed consent form, sex, race/ethnicity, age, height, and body mass index.

Body mass index will be automatically calculated in the eCRF.

12.2.2 Prior and concomitant medication or therapies

All medication requiring prescriptions (including oral contraceptives), over-the-counter medication (including herbals and vitamins), and therapies (including medical devices and therapies such as e.g., massage or cognitive behavioral therapy) used within 3 months prior to enrollment and up to the end of the trial must be recorded in the eCRF. All failed CRPS medication must be added in the eCRF (including medications stopped before 3 months prior to enrollment). Any change in dosage, regimen, frequency, or route, must be recorded in the eCRF as a new entry.

For the concomitant medication, the trade name, dose, dose unit, frequency, route, reason for use, start date, and stop date have to be recorded in the eCRF.

12.2.3 Relevant prior/concomitant disease or surgical interventions

All medical history relevant to CRPS (including family history of CRPS) should be documented in the eCRF (for details, see Section 12.2.3.1). Additional medical history for the previous 3 years as well as medical history from prior to 3 years that may be considered relevant should also be documented in the eCRF.

There is no requirement to obtain copies of medical records from treating physicians to document medical history.

12.2.3.1 Diagnosis of CRPS

Diagnosis of CRPS according to the clinical diagnostic criteria in [Table 4](#) must be documented at the Enrollment Visit upon examination of the subject. It is the absolute responsibility of the investigator to make the diagnosis of CRPS according to the correct diagnostic criteria. Application of the CRPS diagnostic criteria requires identification of an affected limb. Distal to mid-limb involvement (typically hand or foot), with or without proximal spread, must be present. Evidence of asymmetrical signs and symptoms, relative to the contralateral (less affected) limb, is a requirement for fulfilling the diagnostic criteria. A precise location of the CRPS, consistent with the location of signs and symptoms, must be documented in the eCRF. If more than 1 limb is considered to be affected, the trial-designated CRPS most affected-limb must be readily distinguished based on asymmetrical signs and symptoms, relative to the contralateral limb, and the subject must be able to differentiate pain in the affected limb from pain in any other affected limbs. Ongoing, disproportionate pain and a lack of other diagnosis that better explains the signs and symptoms must also be confirmed at the Enrollment Visit.

Diagnosis of CRPS involving an atypical body part (e.g., trunk, breasts, pelvic region, lower back, face, shoulder, or hip) is not permitted for this trial.

Table 4: Complex regional pain syndrome clinical diagnostic criteria recommended by the IASP; “Budapest clinical criteria”

-
1. Continuing pain, which is disproportionate to any inciting event.
 2. Must report at least one symptom in *three of the four* following categories:
 - Sensory: reports of hyperesthesia and/or allodynia.
 - Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry.
 - Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry.
 - Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).
 3. Must display at least one sign at time of evaluation in *two or more* of the following categories:
 - Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement).
 - Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry.
 - Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry.
 - Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).
 4. There is no other diagnosis that better explains the signs and symptoms.
-

IASP = International Association for the Study of Pain.

Source: Harden et al. 2010a

In accordance with procedures for validation of these criteria, symptoms will be assessed with a recall period “since the onset of CRPS”. Signs must be present, i.e., observed by the examiner, during the evaluation at the Enrollment Visit. Subjects will be examined for 8 signs (observed on examination, yes or no): hyperalgesia to pinprick; allodynia (light touch, deep joint pressure, vibration, cold, and heat); temperature asymmetry by palpation (affected side cooler or warmer than the contralateral side); skin color asymmetry (red, blue or pale, mottled, or scar); asymmetric edema; sweating asymmetry (increased or decreased on the affected side); dystrophic changes (nails, hair, or skin); and motor changes (tremor, dystonia, decreased AROM, or weakness).

Medical history related to CRPS must include the following: date and description of precipitating event (e.g., type of trauma, surgery [including any information on whether there was a major nerve injury]; if no precipitating event is known, document as unknown), the specific location of CRPS, including the affected limb (if more than 1 limb is affected, the most painful limb as well as any other affected limb must be identified), the date of onset of symptoms, the date of CRPS diagnosis, and the type of CRPS (CRPS-I or CRPS-II). Any documentation supporting the diagnosis of CRPS, including any assessments used to rule out alternative diagnoses, will be retained.

12.2.3.2 Dental history

Dental history will include the date of last dental visit; dental extractions and other invasive dental surgery in the past 3 months prior to the Enrollment Visit; current evidence of dental or periodontal disease, gum injury due to dentures, or other dental history that may pre-dispose to risk of medication-related osteonecrosis of the jaw.

12.2.4 Other baseline characteristics

12.2.4.1 Physical examination

Physical examination should include assessments of the general condition, skin, eyes, ears, nose and throat, mouth (including teeth and gums), head, neck, and thyroid, heart, lung, chest, abdomen, kidneys, liver, lymphatic, musculoskeletal, and neurological systems.

Prior to allocation to treatment, any clinically relevant findings from the physical examination will be documented as part of the medical history.

12.2.4.2 Urine drugs of abuse test

Urine samples will be provided by the subject at Visit 1 and Visit 2 (and Visit 11 for subjects going into Treatment Period B) for local testing for drugs of abuse using a urinary dipstick (performed at the site). Only test results for the following drugs of abuse will be recorded in the eCRF:

- Cocaine, MDMA (3,4-methylenedioxy methamphetamine, ecstasy), amphetamines, cannabinoids.

Subjects who are receiving stable doses of prescribed medications containing amphetamines, benzodiazepines, cannabinoids, or opioids will not be excluded from the trial even if the test is positive.

12.3 Collection of efficacy data

The following efficacy data will be collected: pain intensity, CRPS Severity Score, measurements of edema, DMA, PPT, AROM, PGIC, PGI-S, EQ-5D-5L, PROMIS-29 profile and the PROMIS-EDDEP39, the 6 neuropathic pain items of the SF-MPQ-2, PCS, and PSEQ.

For the timings of assessments, see the schedules of events (Section 1.7).

12.3.1 Pain intensity

Pain intensities will be recorded in electronic diaries at home and on tablet computers maintained at the sites.

12.3.1.1 Electronic diary

Subjects will be 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 will be for a 24-hour recall period.

After Visit 8 up to Visit 17, subjects will be 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.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

Average pain assessment

Subjects will be asked to record their average CRPS-related pain intensity for the previous 24 hours.

The subjects will be asked to answer the following question:

“Please rate your pain by selecting the one number that best describes your pain on average during the last 24 hours.”

Worst pain assessment

Subjects will be asked to record their worst CRPS-related pain intensity for the previous 24 hours.

The subjects will be asked to answer the following question:

“Please rate your pain by selecting the one number that best describes your pain at its worst during the last 24 hours.”

Current pain assessment

Subjects will be asked to record their current CRPS-related pain intensity.

The subjects will be asked to answer the following question:

“Please rate your pain by selecting the one number that best describes how much pain you have right now.”

12.3.1.2 Site tablet computer

At the visits indicated in the schedules of events (Section 1.7), the subjects will be asked to record the pain intensity ratings for average, worst, and current CRPS-related pain directly on a tablet computer maintained at the site. Worst and average pain intensity ratings in this case will be based on a 24-hour recall period.

Average pain assessment

Subjects will be asked to record their average CRPS-related pain intensity for the previous 24 hours.

The subjects will be asked to answer the following question:

“Please rate your pain by selecting the one number that best describes your pain on average during the last 24 hours.”

Worst pain assessment

Subjects will be asked to record their worst CRPS-related pain intensity for the previous 24 hours.

The subjects will be asked to answer the following question:

“Please rate your pain by selecting the one number that best describes your pain at its worst during the last 24 hours.”

Current pain assessment

Subjects will be asked to record their current CRPS-related pain intensity.

The subjects will be asked to answer the following question:

“Please rate your pain by selecting the one number that best describes how much pain you have right now.”

12.3.1.3 Pain intensity question of the PROMIS-29 profile

At Visit 11, the pain intensity question (question number 29, GLOBAL07) of the PROMIS-29 profile (Section 18.3.4) will be used as 1 of the criteria for continuing into Treatment Period B. At Visit 9 and Visit 10 the PROMIS pain question will be used to monitor efficacy.

The subjects will be asked to answer the following question on an 11-point NRS (0 = no pain, 10 = worst imaginable pain):

“In the past 7 days, how would you rate your pain on average?”

12.3.2 Dynamic mechanical allodynia

Allodynia is defined as pain in response to a non-nociceptive stimulus. In cases of mechanical allodynia, even gentle mechanical stimuli such as a slight bending of hairs can evoke pain. The DMA is assessed by the investigator, documented in the source data, and transferred to the eCRF. A Q-tip fixed to an elastic strip exerting a force of 100 mN (Ziegler et al. 1999) is applied in a single sweeping motion (1 cm to 2 cm length) on the skin of the affected limb.

The subjects are asked to judge the stimulus intensity on an NRS (0 to 10), with “0” in this case meaning “no pain”, while each “pricking”, “stinging” or “burning” sensation is defined as a painful sensation, being evaluated by giving a value greater than “0”. A value of “10” corresponds to the individual maximum pain imaginable. The tactile stimulus is tested 5 times. If the subject reports a value of “10”, then no further test will be performed for the respective visit. The degree of pain sensitivity is calculated by the geometrical mean of the pain ratings given (Maier et al. 2010).

12.3.3 Pressure pain threshold

The PPT is assessing the level of pressure causing deep joint or muscle pain. In CRPS subjects, light, normally non-painful pressure applied at joints or muscles causes pain in the deep somatic tissues (Baron et al. 2010). The PPT is assessed by the investigator on both affected and unaffected limbs by using a pressure algometer (contact area 1 cm²), documented in the source data, and transferred to the eCRF. The threshold for pressure induced pain is measured on the thenar muscle/abductor hallucis muscle, starting with the unaffected limb. Measurements are repeated in 3 series of slowly increasing stimulus intensities (at a rate of about 50 kPa/s). The subject must not be able to look at the readings during the measurement. Data are averaged for the each of the 3 series of measurements. For the final PPT, the arithmetic mean of all 3 consecutive measurements is calculated (Rolke et al. 2010 and Mainka et al. 2014).

The ratio of the thresholds of the affected and the unaffected limb will be calculated.

12.3.4 Edema measurement

Edema will be measured by the investigator with measurement tape using the figure-of-eight method at both the affected and contralateral unaffected limb for all subjects having edema as a positive CRPS sign at baseline (based on clinical judgment; sign “Asymmetric edema” ticked “yes” on the CRPS Severity Score at Visit 2) and will be documented in the source data and transferred to the eCRF. At each visit, first the unaffected limb has to be measured to accustom the subject to the measurements, followed by the affected limb. Each measurement of the limbs 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 and the unaffected limb will be calculated.

Detailed instructions and training describing in depth the figure-of-eight method for measuring edema in both hands or feet will be provided to the investigators.

12.3.5 Active range of motion measurement

The AROM is the range of movement through which a subject can actively (without assistance) move a joint using the adjacent muscles. Measuring the AROM does not involve any external stimulation; the subject is not touched and decides how far to move. The magnitude of the AROM can be influenced by other factors not directly related to the joint, such as the subject’s motivation. In order to maximize the reliability of measurements, a rigid measurement protocol and valid and reliable measurement instruments were developed. Detailed instructions and in depth training will be provided to the investigators.

The subject has to be instructed not to exceed the pain limit in order to avoid increase of complaints, which could influence future measurements and treatment outcome.

For subjects having decreased AROM at baseline (diagnosed based on clinical judgment; sign “Motor abnormalities” ticked “yes”, sub-category “decreased AROM” ticked “yes” on the CRPS Severity Score at baseline [Visit 2]), both affected and unaffected limbs will be measured using a goniometer, first the unaffected extremity to accustom the patient to the measurements, followed by the affected extremity. The AROM is measured only during active flexion and extension (i.e., sagittal plane, transversal axis) of the wrist or ankle, respectively.

The AROM in each of the unaffected and affected limbs will be measured 2 times. The results of both measurements will be documented; only the best performance of the 2 repetitions will be used for further analysis.

The ratio of the AROM of the affected and the unaffected limb will be calculated.

12.3.6 CRPS Severity Score

Signs and symptoms of CRPS (Section 18.4) will be assessed by the investigator and recorded using the tablet computers maintained at the sites. Subjects will be queried on 8 self-reported symptoms (queried yes or no): continuous, disproportionate pain; allodynia and/or hyperalgesia; temperature asymmetry; color asymmetry; sweating asymmetry; edema; dystrophic changes; and motor abnormalities. Symptoms will be assessed based on a recall period of 48 hours. Subjects will be examined for 8 signs (observed on examination, yes or no): hyperalgesia to pinprick; allodynia; temperature asymmetry by palpation; skin color asymmetry; sweating asymmetry; asymmetric edema; dystrophic changes; and motor changes (please refer to Section 12.2.3.1 and Section 18.4

for the description of the signs and symptoms). Each sign or symptom is assigned a dichotomous value (1 = presence; 0 = absence). The resulting score ranges from 0 to 16, with higher scores indicating greater CRPS severity (Harden et al. 2010b).

12.3.7 Patient Global Impression of Change

The PGIC will be assessed using the tablet computers maintained at the sites. The 7-point PGIC is a complementary assessment of analgesic efficacy. Subjects respond to the question “Since the start of the trial, my overall status is:” with 1 of 7 possible responses (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse; Section 18.3.1). A response of very much improved or much improved is generally regarded as a clinically important outcome. As “change” is conceptually inherent in the questionnaire, no baseline assessment can be performed.

12.3.8 Patient Global Impression of Severity

The PGI-S will be assessed by the subjects using the tablet computers maintained at the sites. The 5-point PGI-S is a 1-item questionnaire designed to assess a patient’s impression of disease severity.

Subjects are asked to best describe their CRPS symptoms over the past week with 1 of 5 possible responses (none, mild, moderate, severe, very severe; Section 18.3.2).

12.3.9 EuroQoL-5 dimension-5 level

The EQ-5D-5L health questionnaire (Section 18.3.3) will be completed by all subjects using the tablet computers maintained at the sites. The EQ-5D-5L has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the 5 dimensions has 5 possible levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. An index (total) score will be calculated from data from all 5 dimensions using an index value calculator that can be downloaded from the EuroQoL website. For the US general population, the possible EQ-5D-5L index scores range from -0.109 (i.e., 55555) to 1.0 (i.e., 11111) on a scale where 0.0 = death and 1.0 = perfect health. The EQ-VAS ranges from 0 (worst imaginable health) to 100 (best imaginable health). A higher score represents better overall health.

12.3.10 PROMIS-29 profile and the PROMIS-EDDEP39

The PROMIS-29 profile (Section 18.3.4) assesses 7 domains, i.e., depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles and activities, each with 4 questions and a recall period of 7 days (Cella et al. 2007).

The PROMIS-29 Profile version 2.0 will be completed by the subjects using the tablet computers maintained at the sites.

In addition, suicidal ideation will be assessed using the PROMIS-EDDEP39 (Section 18.3.5), which is Question EDDEP39 of the PROMIS Item Bank version 1.0 – Emotional Distress – Depression (Pilkonis et al. 2011).

12.3.11 Short-Form McGill Pain Questionnaire 2: 6 neuropathic pain items

The SF-MPQ-2 is a single measure of the major symptoms of both neuropathic and non-neuropathic pain. The pain qualities will be assessed using the 6 neuropathic items from the SF-MPQ-2 (Section 18.3.6).

Subjects will be asked to consider and report only the pain related to the CRPS when completing the instrument using the tablet computers maintained at the sites.

12.3.12 Pain Catastrophizing Scale

The PCS (Section 18.3.7) will be used as a measurement tool to capture pain catastrophizing; the scale will be completed by the subjects using the tablet computers maintained at the sites.

12.3.13 Pain Self Efficacy Questionnaire

The PSEQ (Section 18.3.8) will be used to capture pain self-efficacy and is completed by the subjects using the tablet computers maintained at the sites.

12.4 Collection of safety data

The following safety data will be collected: adverse events, vital signs, 12-lead ECGs, safety laboratory parameters, physical examination findings, and urine β -HCG pregnancy test outcome.

For the timings of assessments, see the schedules of events (Section 1.7).

Clinically relevant abnormal values (investigator's judgment) must be recorded as adverse events.

12.4.1 Adverse events

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

Definition of adverse events

An adverse event is any untoward medical occurrence in a subject enrolled in a clinical trial. An adverse event can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Pre-existing diseases or conditions occurring before enrollment are not considered to be adverse events unless there is an untoward change in intensity, frequency, or quality after enrollment.

Lack of efficacy, as such, is not considered to be an adverse event while its consequences (e.g., deterioration of the treated disease) are considered to be an adverse event.

A newly diagnosed pregnancy of an enrolled female subject will not be considered an adverse event itself unless it is suspected that the trial treatment interacted with a contraceptive method. In this case, the pregnancy will be considered an adverse event. A congenital anomaly as an outcome of a pregnancy will be considered a serious adverse event (SAE).

All newly diagnosed pregnancies of enrolled female subjects must be reported to the sponsor's Drug Safety Department within 24 hours after first knowledge. These pregnancies will be

documented using a pregnancy reporting form with all available information provided and followed up to determine the outcome post parturition.

For newly diagnosed pregnancies of partners of enrolled subjects, a reasonable attempt (i.e., due diligence) must be made to report the pregnancy to the sponsor's Drug Safety Department within 24 hours after first knowledge.

Definition of serious adverse events

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is considered a clinically important medical event. The medical concepts included in Section 18.1 should be taken into account when applying this seriousness criterion.

An elective hospital admission, e.g., for pre-planned surgery, will not be considered an SAE if documented at enrollment. Short-lasting (<24 hours) hospital admissions, e.g., for clinical check-ups, not meeting any of the other above mentioned criteria will also not be considered SAEs.

Special procedures for serious adverse events

If SAEs occur that are not tolerable, the investigator will decide whether to stop the trial participation and/or treatment of the subject. For further details, see Section 9.3.

Expectedness of adverse events

Expectedness will be assessed by the sponsor.

An unexpected adverse event is one where the nature or intensity is not consistent with the information in the neridronic acid investigator's brochure.

Furthermore, reports that add significant information about the specificity or severity of a known, already documented adverse reaction constitute unexpected adverse events. For example, an adverse event more specific or more severe than expected would be considered "unexpected".

Definition of adverse drug reactions

An adverse drug reaction is any untoward and unintended response to an IMP or a medicinal product related to any dose administered.

A list of adverse drug reactions seen for the IMP is given in the reference safety information (neridronic acid investigator's brochure).

Documentation of adverse events

The subjects will be questioned about possible adverse events with non-leading questions before administration of the IMP and at regular intervals thereafter as defined in Section 1.7.

All adverse events reported spontaneously by subjects at any time point will also be documented.

All adverse events will be documented in the eCRF with the following information where appropriate:

- Description (adverse event reported term).
- Start date/time.
- End date/time or continuation.
- Whether adverse event was serious.
- Intensity.
- Outcome.
- Action taken with IMP.
- Countermeasures.
- Causal relationship to IMP.

Definition of intensity

The clinical intensity of an adverse event will be classified as:

Mild:	Signs and symptoms that can be easily tolerated. Symptoms can be ignored and disappear when the subject is distracted.
Moderate:	Symptoms cause discomfort but are tolerable; they cannot be ignored and affect concentration.
Severe:	Symptoms which affect usual daily activity.

For adverse events where the intensity changes over time, the maximum intensity observed during the whole duration of the adverse event will be documented.

Adverse events occurring in the Enrollment Period but before first administration of an IMP and worsening on or after IMP administration will be documented as new adverse events.

Definition of outcome at the time of last observation

The outcome at the time of last observation will be classified as:

- Recovered/Resolved.
- Recovering/Resolving.
- Not recovered/Not resolved.
- Recovered/Resolved with sequelae.
- Fatal.
- Unknown (unknown should only be used, if at the time of the last visit for a subject in a trial, the outcome of the adverse event is unknown to the investigator, e.g., because the subject is lost to follow-up).

Definition of countermeasures

“Countermeasures” will be defined as:

None:	No countermeasure given.
Newly started medication:	A newly started medication or change in dose or route of application of a medication due to the adverse event (to be listed on the prior/concomitant medication page) that is used

	as a countermeasure.
Trial discontinuation:	It was necessary to discontinue the subject from the trial due to the adverse event.
Other:	All other countermeasures, e.g., physical therapy, surgery.

Except for none, multiple countermeasures for 1 adverse event can be recorded.

Classification of action taken with IMP when an adverse event occurs:

- Dose not changed.
- Drug interrupted.
- Drug withdrawn.
- Not applicable.
- Unknown.

Classification of causation

The causal relationship of an adverse event to IMP will be classified using the following terminology. The given criteria for each term are for consideration and are neither exhaustive nor required to be fulfilled in total for the selection of the respective term:

Terms for classification of causation	Criteria for the selection of causality classification terms
Conditional/Unclassified:	Additional data for a proper assessment are under examination.
Unassessable/Unclassifiable:	The available data cannot be judged because information is insufficient or contradictory, and cannot be supplemented or verified.
Not related:	Data with sufficient evidence to accept that there is no causal relationship to IMP administration (i.e., there is no temporal relationship to IMP administration or proved other cause).
Unlikely:	Data without sufficient evidence to accept that there is no causal relationship to IMP administration, but also with no evidence or argument to suggest a causal relationship (e.g., the temporal relationship to IMP administration makes a causal relationship improbable, and other drugs, chemicals, or underlying disease[s] provide plausible explanations).
Possible:	Data with limited evidence or argument to suggest a causal relationship (e.g., there is a reasonable time sequence to administration of the drug, but the adverse event could also be explained by concurrent disease[s] or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear).
Probable/likely:	Data with sufficient evidence or argument to suggest a causal relationship (e.g., there is a reasonable time sequence to administration of the drug, the adverse event is unlikely to be attributed to concurrent disease[s] or other drugs or chemicals, and a clinically reasonable response on withdrawal [dechallenge]).
Certain:	Data with clear evidence for a causal relationship (i.e., a clinical event, including laboratory test abnormality, occurs in a plausible time relationship to drug administration, and it cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug [dechallenge] should be well defined and clinically plausible, using a satisfactory rechallenge procedure if appropriate).

Follow-up of subjects with an adverse event

Any adverse event or clinically relevant abnormal laboratory or vital sign result will be followed until it reaches a satisfactory resolution, or becomes stable, or clinical judgment indicates that further evaluation is not warranted.

Notification of serious adverse events

All SAEs (including death, irrespective of cause during the trial, regardless of their relationship to IMP, must be reported as soon as possible but no later than 24 hours after learning of the event. Before any trial-related procedure is performed, the trial site must be provided with contact details at the sponsor's Drug Safety Department for this reporting.

The investigator must submit a report, called a safety reporting form, which includes a description of the event, the therapy instituted, and trial procedures. The following information should be communicated with the first notification of an SAE:

- Trial identifier.
- Subject's identifier.
- Subject's date/year of birth (if available, see local data protection requirements) or age (at adverse event onset).
- Subject's sex.
- First administration of IMP (date and time, if available).
- Last administration of IMP (date and time, if available).
- Adverse event verbatim term (specific diagnosis, if possible).
- Adverse event onset (date and time, if available).
- A brief description of the event, the course, and the countermeasures taken.
- Intensity.
- Seriousness criterion.
- Outcome.
- Concomitant medication at onset of the event and whether one of the concomitant medications is also suspected to have caused the event.
- Relevant history/pre-existing medical conditions.
- Investigator's assessment of the relationship to IMPs.
- Whether and when blinding was broken.

All additional information concerning the adverse event until trial termination or definite outcome must be communicated per follow-up report without delay.

The immediate and follow-up reports must only identify the subjects using the unique subject identifier.

The investigator must comply with applicable regulatory requirement(s) related to the reporting of SAEs to the regulatory authorities and the relevant IECs or IRBs.

Notification of serious adverse reactions

All suspected adverse drug reactions related to an IMP (the tested drugs and comparators) that occur in this trial, and that are both unexpected and serious are subject to expedited reporting.

Once a year throughout the clinical trial, the sponsor will provide the member states in whose territory the clinical trial is being conducted and the IECs with a listing of all suspected unexpected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

In addition, the sponsor will ensure that all reportable events are reported in compliance with applicable international and national regulatory requirements.

12.4.2 Vital signs

The vital signs comprise systolic and diastolic blood pressure, pulse rate, and respiratory rate.

Vital signs will be measured in a sitting position after resting for 10 minutes. While resting, the subject should not receive anything to drink or eat.

12.4.3 Body weight

Body weight will be measured in light clothes.

12.4.4 Twelve-lead electrocardiogram

All ECGs will be recorded in triplicate (3 readings in rapid succession no more than 2 minutes apart).

The times at which the ECGs were recorded will be documented in the eCRF.

The 12-lead ECG recordings will be performed after the subjects have been in a supine position for at least 10 minutes in a quiet environment without exciting distractions (e.g., television, video games). The recording should include a minimum of 5 heart cycles (beats).

Electrocardiographic parameters (heart rate; P, QRS, and T waves; PR, QT, and QTcF intervals), and waveform morphology will be evaluated by the investigator. The investigator will be responsible for determining the clinical relevance of any abnormality and deciding whether a subject can continue in the trial with the observed findings. The investigator will be required to comment any abnormalities with reference to any possible clinical relevance.

A central ECG reading facility will provide the results of the ECG interval measurements and an assessment and interpretation of any waveform abnormalities and other findings (e.g., conduction defects). The investigator will be informed of the results and must evaluate them in the context of the subject's characteristics. The investigator will be required to comment any abnormalities with reference to any possible clinical relevance. The investigator will also make a decision whether the subject should continue in the trial or whether further ECGs or investigations should be performed to clarify and ensure the safety of the subject.

Electrocardiograms with poor quality tracings, artifacts or doubtful findings should be repeated, if possible.

For decisions relating to subject exclusion or discontinuation of IMP, the investigator's initial evaluation will be used.

The evaluation from the central ECG reading facility will be used for the assessment and analysis of ECG parameters and for evaluation of any tendency regarding changes in ECG parameters for the final integrated clinical trial report.

The ECG measurements and the findings, if any, from the central ECG evaluation together with the overall assessment of the clinical relevance by the investigator will be captured in the database.

The original ECG recordings will be kept at the trial site.

The ECG files including the waveforms and caliper placements will be provided electronically as xml files to the sponsor at the end of the trial.

12.4.5 Safety laboratory

Safety laboratory tests (except for urine dipsticks for urinalysis, semi-quantitative urinary ACR determination, urine drug testing, and urine pregnancy testing) will be performed by a central laboratory.

The use of any laboratory facility other than the designated laboratory for safety laboratory tests required by this protocol is not allowed. The only exception is in the case of an emergency where the investigator requires the results quickly.

A table of the reference ranges for each of the laboratory parameters measured with a description of the methods will be provided by the laboratory before the trial start and is to be filed in the investigator's site file.

Changes in the reference ranges or in the methodology during the course of the trial are to be communicated by the laboratory to the sponsor who will inform the investigators.

The trial sites will be provided with a manual by the laboratory specifying the specimen collection, preparation, packaging, and transport of all safety laboratory tests required by this protocol.

Throughout the clinical part of the trial, the investigator must provide a comment in the eCRF regarding the clinical relevance of any laboratory values outside the sponsor-defined alert range.

Results for the laboratory parameters defined below will be sent electronically to the trial site and transferred electronically to the data management provider where these electronic data will be integrated into the clinical database. The clinical database will be transferred to the sponsor.

The following tests will be performed:

Hematology panel	
Erythrocytes	Leukocytes (including basophils, eosinophils, lymphocytes, monocytes, and neutrophils if a differential count is performed)
Hematocrit	Platelets
Hemoglobin	

Clinical chemistry panel

Alanine aminotransferase	Magnesium
Albumin	Parathyroid hormone ^a
Alkaline phosphatase	Phosphate
Aspartate aminotransferase	Potassium
Bilirubin (total)	Protein (total)
Calcium (measured and albumin-corrected)	Sodium
Creatine kinase	Triacylglycerol lipase
Creatinine	Urea
Gamma glutamyl transferase	Uric acid
Glucose (non-fasted or fasted)	Vitamin D
Lactate dehydrogenase	

a) Enrollment Visit only.

The eGFR will be calculated using the 2009 CKD-EPI creatinine equation (Levey et al. 2009).

Urinalysis panel

Dipstick	Semi-quantitative dipstick	Quantitative analysis
Bilirubin	Urinary albumin/creatinine ratio	Albumin (microalbumin)
Erythrocytes		Creatinine
Glucose		Calculated urinary albumin/creatinine ratio
Ketones		
Leukocyte esterase		
Nitrite		
pH		
Protein		
Urobilinogen		

If the dipstick test is positive except for pH, glucose or ketones and erythrocytes/leukocytes in menstruating subjects, a microscopic examination of urine sediment will be performed to determine the presence of erythrocytes, leukocytes, epithelial cells, crystals, casts, bacteria, and other findings.

The number of samples and volume per sample collected from each subject for safety laboratory analysis are given in [Table 3](#).

If laboratory values of liver parameters exceed pre-defined ranges (a combination of alanine aminotransferase and/or aspartate aminotransferase greater than 3 times the upper limit of normal and/or bilirubin greater than 2 times the upper limit of normal) after first application of IMP, a standard algorithm to detect and follow-up on potential severe cases of drug-induced liver injury will be applied (see Section 18.2).

12.4.6 Physical examination

After treatment allocation, any clinically relevant changes from the previous visit for physical examination will be documented as adverse events.

12.4.7 Urine beta-human chorionic gonadotropin pregnancy test

Urine samples will be provided by women of child-bearing potential at the specified times and tested locally using a urine β -HCG pregnancy dipstick test.

The results of the dipstick test will be directly entered into the eCRF.

Additional pregnancy tests to those specified may be performed if required by local law or regulations.

Pregnancy testing may be requested from the central laboratory.

12.5 Collection of plasma concentration data

12.5.1 Blood sampling for bioanalysis

Details of the blood sample collection times for plasma concentrations are given in the schedules of events (Section 1.7).

The exact sampling time must be recorded in the eCRF.

The blood samples for plasma concentrations will be collected via single venipuncture or an indwelling cannula. If required, a mandrin will be used to maintain the patency of the catheter for the blood sampling. **Blood sampling must be performed from the contralateral arm to the one used for infusion or other appropriate location to avoid any possibility of contamination. Blood samples obtained during infusions must not be taken from the same access as used for IMP administration.**

Further instructions for the blood sample collection and handling, labeling, and shipping are given in the laboratory manual, which will be supplied to the investigator.

The number of samples, volume per sample, and total blood volume collected are given in [Table 3](#).

12.5.2 Bioanalytical assays

Plasma samples will be analyzed to determine concentrations of neridronic acid using a validated bioanalytical assay under the supervision of the department of pharmacokinetics at the sponsor.

Following completion of these assays, the residual samples will be retained until the end of the trial.

The bioanalytical report (PK1769A), including a description of the assay and a summary of the assay performance data, will be included in the final integrated clinical trial report.

12.6 Collection of pharmacodynamic data

12.6.1 Bone turnover markers

Details of the blood sample collection times for the bone turnover markers are given in the schedules of events (Section 1.7). Samples should be collected in the morning after an overnight

fast due to diurnal variation and effects of a meal. Serum concentrations will be determined for the following bone turnover markers:

- Bone formation markers:
 - Procollagen type I amino-terminal propeptide.
 - Bone alkaline phosphatase.
- Bone resorption marker:
 - C-terminal telopeptide of type I collagen.

Specific procedures for preparation of serum samples and storage and shipment will be provided to the sites.

12.7 Collection of markers for disease severity or progression of CRPS

12.7.1 Soluble interleukin-2 receptor (sIL-2R)

Details of the blood sample collection times for the analysis of sIL-2R are given in the schedules of events (Section 1.7).

Specific procedures for the preparation of the plasma samples and instructions for storage and shipment will be provided to the sites.

12.8 Collection of pharmacogenetic and omics data

Blood samples for storage and pharmacogenetic and omics testing will be collected into plastic ethylenediaminetetraacetic acid (EDTA) tubes from consenting subjects at the times given in the schedules of events (Section 1.7). The blood samples will be labeled with the trial code and subject number (and, if appropriate, using a bar code). They will not carry any personal identifier (i.e., single-coded data or double-coded data as described in ICH topic E15 2008).

The blood samples will initially be sent from the trial site to a temporary storage site qualified by the sponsor for short-term storage. The samples will then be transferred in batches from the temporary storage site to the bio-banking facility qualified by the sponsor for long-term storage.

Following extraction of DNA from the pharmacogenetic blood samples, the DNA will be stored in appropriate containers and labeled with a trial code and subject number (and, if appropriate, using a bar code). For omics, the plasma samples will be stored.

They will not carry any personal identifier (i.e., they will be double-coded data as described in ICH topic E15 2008). The DNA samples will be stored at the external bio-banking facility for up to 15 years after completion of the trial (defined as the date of approval of the integrated clinical trial report in the sponsor's document management system) to allow for pharmacogenetic testing. After 15 years of storage, the DNA and plasma samples will be destroyed.

12.9 Collection of health economics outcome and work productivity data (US sites only)

12.9.1 Work Productivity and Activity Impairment Questionnaire: CRPS

History of CRPS including impairments of personal activities, both work-related (e.g., absenteeism/presenteeism) and non-work-related will be captured using the WPAI: CRPS (Section 18.3.9).

The WPAI questionnaire is an instrument to measure impairments in both paid work and unpaid work (Reilly et al. 1993). It measures absenteeism and presenteeism as well as the impairments in unpaid activity because of health problems during the past 7 days.

The WPAI: CRPS will be assessed using the tablet computers maintained at the sites at the time points given in the schedules of events (Section 1.7).

12.9.2 Medical resources utilization and health economics data collection

Medical resource utilization and health economics data will include information regarding hospitalization, emergency room visits, nursing home stays, health care provider (other than trial investigator) contacts, home services, home help, and special devices used due to CRPS-related symptoms and pain. Data will be collected at the time points given in the schedules of events (Section 1.7).

The questions to be asked by the investigator are provided in Section 18.5.

The responses to the questions will be documented on paper and stored as part of the source data. Data will be transcribed into the eCRF by the investigator or delegated site staff.

12.10 Appropriateness of measurements

Efficacy assessments

As CRPS is a rare, poorly understood chronic pain syndrome condition with very few adequate and well-controlled trials having been conducted, the proposed outcome measures for this trial have not been formally validated in this population.

The efficacy assessments chosen for this trial reflect the core outcome measures for CRPS clinical trials (COMPACT). These were developed by an international consortium of patients, clinicians, researchers and industry representatives to develop and agree on a minimum core set of standardized outcome measures for use in future CRPS clinical trials in an adult population (Grieve et al. 2017). The key concepts identified were pain, disease severity, participation and physical function, emotional and psychological function, self-efficacy, catastrophizing and PGIC. The final core measurement set included the optimum generic or condition-specific patient-reported questionnaire outcome measures, which captured the essence of each domain.

Numerical rating scale for pain

The unidimensional 11-point NRS is a recommended method of assessing pain intensity in subjects with various types of chronic pain (CPMP/EWP/252/03 Rev. 1).

On the basis of IMMPACT recommendations for core outcome measures in chronic pain studies, the 11-point NRS was chosen as the primary efficacy outcome measure (Dworkin et al. 2005). The NRS is a standard, widely used tool for the assessment of pain (Dworkin et al. 2008). Average, worst, and current pain intensity will be assessed.

For subject-reported outcomes captured electronically, the system will ensure data integrity by allowing only subjects to enter the data (electronic diary, tablet computer at the site). Electronic subject-reported outcome systems ensure that neither sponsors nor investigators can access and change the data, and subjects cannot enter data retrospectively or in advance, i.e., the timing of entries is controlled and compliance is enforced. Additionally, no data are lost because of illegible handwriting. As required by the FDA Guidance for Industry 2009 on the use of subject-reported outcomes, the database for the electronic patient-reported outcomes uses a regular back-up and does not allow access to unblinded data.

Subjects report little difficulty with electronic patient-reported outcome system procedures and are not unduly burdened by their use resulting in good reporting compliance (Stone et al. 2004).

Dynamic mechanical allodynia

Allodynia is a positive sign identified by physicians in about 70% of CRPS patients and a self-reported symptom by almost 90% of the CRPS patients (Harden et al. 2010b). The DMA measurement is part of the Quantitative Sensory Testing protocol developed by the German Research Network on Neuropathic Pain as a comprehensive battery of sensory tests to quantify functions of the human somatosensory nervous system (Maier et al. 2010).

Pressure pain threshold

The PPT aims to quantify the mechanical deep somatic hyperalgesia in CRPS patients. Many patients with CRPS report pain in the depth of the limb rather than superficially in the skin, pointing to the importance of deep somatic structures such as bones, joints, tendons, and muscles in the pathophysiology of CRPS (Mainka et al. 2014).

Pain localized in the deep tissues occurs frequently in CRPS. In addition, hyperalgesia to blunt pressure over muscles is common in CRPS. The PPT over the thenar muscle provides 77% sensitivity and 63% specificity in identifying a patient with CRPS (cutoff 293 kPa; Mainka et al. 2014).

Edema measurement - figure-of-eight method

Edema is a sign identified by physicians in about 65% of CRPS patients and a self-reported symptom by almost 90% of the CRPS patients (Harden et al. 2010b). Quantifications of edema are used to establish a baseline at the initial examination and to document changes in subject status. The figure-of-eight is a method of measuring edema by means of measuring tape and pre-defined anatomical landmarks. It demonstrated high intra-rater reliability, inter-rater reliability, and concurrent validity (Pellecchia 2003, Leard et al. 2004, dos Reis et al. 2004).

Active range of motion - goniometry

Decreased AROM is a sign identified by physicians in and a self-reported symptom by about 86% of CRPS patients (Harden et al. 2010b). The AROM is measured using an universal hand-held goniometer, based on the guidance recommended by the American Medical Association guidelines

and by the American Society of Hand Therapists' clinical assessment recommendations. The AROM was applied for subjects with CRPS by Perez et al. 2003 and Oerlemans et al. 1998.

Possible threats to the reliability of the AROM measurements (more than one rater, [in]experience of the rater [unstructured] measurement protocols) have to be controlled for by using a rigid measurement protocol, valid and reliable measurement instruments, and, where possible, the same rater performing the initial and subsequent measurements for 1 subject (Perez et al. 2003).

CRPS Severity Score

The CRPS Severity Score has been shown to discriminate well between CRPS and non-CRPS patients and displayed strong associations with dichotomous CRPS diagnoses using both IASP diagnostic criteria and proposed revised criteria (Harden et al. 2010b). A higher CRPS Severity Score was associated with significantly higher clinical pain intensity, distress, and functional impairments, as well as greater bilateral temperature asymmetry and thermal perception abnormalities. Changes in the CRPS Severity Score show a strong correlation to changes seen in measures for depression and pain scores (Sayyad et al. 2011).

The following outcome measures selected for this trial were based on clinical outcome measures used in interventional trials in more common chronic pain conditions.

Patient Global Impression of Change

The 7-point PGIC is a subject-reported outcome measure tied to the conceptual framework of overall improvement. It is a recommended and responsive outcome domain for pain-related clinical trials (Dworkin et al. 2005, Farrar et al. 2001).

Patient Global Impression of Severity

The PGI-S is a global index that may be used to rate the severity of a specific condition (a single-state scale). It is a simple, direct, easy-to-use scale that is intuitively understandable to clinicians (Yalcin et al. 2003).

EuroQol-5 dimension-5 level

The EQ-5D-5L health questionnaire is a generic health-related quality of life instrument developed by a multidisciplinary team of European researchers. It provides a simple descriptive profile and a single index value that can be used in the clinical and economic evaluation of health care and in population health surveys to assess health outcome from a wide variety of interventions. The EQ-5D-5L is widely used in different countries by clinical researchers in a variety of therapeutic areas.

PROMIS-29 profile

The PROMIS is an existing item bank of patient-reported outcome measures (Cella et al. 2007). It is a National Institute of Health (United States of America) funded system, which provides psychometrically sound and validated patient-reported outcome measures. These can be used in a wide range of chronic conditions. The PROMIS is comprised of calibrated item banks to measure diverse health concepts such as pain, physical function and depression presented for each domain as individual items and/or instruments of various lengths. In addition, PROMIS includes several collections of items, termed profiles, which measure multiple domains.

The PROMIS items can be compared directly with many standard instruments currently employed in clinical trials, such as the 36-item Short-Form Health Survey (SF-36) or Brief Pain Inventory (Choi et al. 2012).

The PROMIS-29 profile is recommended in COMPACT as a measurement tool for core outcome domains of depression, anxiety, physical function, pain interference, fatigue, sleep, and social participation, as well as an additional outcome measure for pain intensity (Grieve et al. 2017). For assessing the suicidal ideation, COMPACT recommends the supplementary use of the PROMIS-EDDEP39.

Short-Form McGill Pain Questionnaire 2: 6 neuropathic items

The SF-MPQ-2 is a single measure of the major symptoms of both neuropathic and non-neuropathic pain. It has excellent reliability and validity, and the results of both exploratory and confirmatory factor analyses provided support for 4 readily interpretable subscales: continuous pain, intermittent pain, predominantly neuropathic pain, and affective descriptors (Dworkin et al. 2009).

The COMPACT consortium recommends the assessment of pain qualities using the 6 neuropathic items from the SF-MPQ-2 as these were considered to capture the essential qualities with minimum patient burden (Grieve et al. 2017).

Pain Catastrophizing Scale

Trials in non-CRPS populations indicate catastrophizing is a prospective predictor of negative pain outcomes. The COMPACT consortium recommends the PCS be used to capture pain catastrophizing (Sullivan et al. 1995): a score of greater than 30 is thought to represent a problematic level of catastrophic thinking (Sullivan et al. 2009). Bean et al. (2016) reported the average PCS score at baseline was 22.0 in their sample of 66 patients diagnosed with CRPS within the previous 12 weeks, but underwent significant reduction to a mean score of 13.4 by 6 months as treatment progressed ($p < 0.001$). This suggests pain catastrophizing as an important outcome and the PCS as a sensitive measurement tool.

Pain Self Efficacy Questionnaire

The PSEQ will be used to capture pain self-efficacy. The respondent considers how confident they are performing each activity, while taking their pain into account. This provides more clinically useful data than asking about performing an activity in isolation (Nicholas 2007). The accumulated evidence from a number of published trials and a confirmatory analysis with a large cohort of heterogeneous chronic pain patients attending a pain management program provide support for the original psychometric properties of the PSEQ developed with a sample of chronic low back pain patients (Nicholas 2007).

Pharmacodynamic assessments

Bone turnover markers

The bone biomarkers CTX (for resorption) and BAP and PINP (for bone formation) have been selected in accordance with recommendations for the selection of these particular biomarkers in other bone diseases, including osteoporosis (Wheater et al. 2013; Vasikaran et al. 2011). Disordered bone metabolism has been suspected in CRPS based on abnormalities observed on imaging (x-rays, bone densitometry and, in particular, bone scintigraphy using radiolabeled bisphosphonates). The

selected markers are known to be responsive to and associated with the mechanism of action of bisphosphonates.

Markers for disease severity or progression of CRPS

Soluble interleukin-2 receptor (sIL-2R)

Interleukin-2 (IL-2) is a cytokine crucially important in regulating activation, proliferation, and survival of different T-cell subsets. This effect of IL-2 is mediated through the IL-2 receptor which consists of the common γ -chain (CD132), a β -chain (CD122), and an α -chain (CD25). CD25 is strongly expressed on activated T-cells, which also secrete this molecule as a soluble variant (referred to as soluble IL-2 receptor; sIL-2R) from the cell membrane into the circulation.

According to Bharwani et al. 2017, plasma sIL-2R levels are significantly elevated in CRPS patients, indicating an increased T-cell activity in CRPS. This finding could point towards a T-cell-mediated inflammatory process in CRPS and sIL-2R could be a potential new marker to determine inflammatory disease activity in CRPS.

Health economics outcome and work productivity data collection

Work Productivity and Activity Impairment Questionnaire: CRPS

The WPAI questionnaire is a well validated instrument to measure impairments in work and activities. It has been validated to quantify work impairments for numerous diseases such as asthma, psoriasis, irritable bowel syndrome, ankylosing spondylitis, Crohn's disease, chronic non-malignant pain, low back pain, and neuropathic pain. In addition, the WPAI questionnaire has been used to compare work impairments between treatment groups in clinical trials or between subjects with different disease severity levels.

Medical resource utilization and health economics data

The data collected by means of this exploratory assessment will support determining the type and frequency of healthcare services used by CRPS patients. This information, correlated with corresponding costs, may be used in developing an evidence-based economic model.

12.11 Compliance

Compliance is the adherence to all requirements of the trial protocol.

Trial site compliance will be assured by the implementation of a quality system and the performance of a combination of trial site visits, training, and monitoring visits. Non-compliance should lead to prompt action by the sponsor to secure compliance.

Compliance of the subjects to record their pain intensity assessments in the electronic diary will be checked by the investigator at the respective visits. A non-compliant subject may be withdrawn from the trial at the discretion of the investigator.

Relevant deviations from the protocol will be documented and described in the integrated clinical trial report.

13 DOCUMENTATION OF TRIAL DATA

The trial documentation must be adequate for the reconstruction of the trial.

13.1 Case report forms

Case report forms for each subject will be provided to the investigator by the sponsor in electronic format to document the trial data.

The investigator and personnel delegated the task will use eCRFs to record information required by the protocol.

All eCRF entries, corrections, and alterations will be made by the investigator or other authorized personnel under their supervision. Entries will be checked against appropriate source documents by authorized sponsor representatives as deemed appropriate in the monitoring guidelines.

The data collection will be done using a validated electronic eCRF system. The collected data will reside on servers of the eCRF provider. Entry, corrections and alterations of data within the system can only be performed by the investigator or other authorized personnel under their supervision and will be captured by the system's audit trail.

Dedicated users (e.g., the investigator, designated persons at the trial site, authorized sponsor representatives, and from other parties involved, e.g., data management) will be trained and receive access rights according to their role in the trial. All users will have access to the system and be able to review their data on an ongoing basis.

After completion of the subject's eCRF, the eCRF must be signed electronically by the investigator. With the investigator's signature it is confirmed that the data in the eCRF are checked, complete, accurate, and in alignment with the source data. Changes to the eCRF after initial signing by the investigator need re-signing.

With database lock, the edit rights to the eCRFs will be removed but the investigator will retain access to view the eCRFs until receipt of a certified copy of all data captured for his or her subjects (site archive). This data will be delivered in a human readable form for retention in his or her files.

13.2 Subject-reported outcomes

Subject-reported outcomes will be collected using a validated electronic patient-reported outcome system including audit trail (electronic diary and site tablet computer).

The investigator will be trained on the use of the electronic patient-reported outcome system and the related oversight system. The oversight system will allow the investigator to review all data entered by the respective site subjects on an ongoing basis.

Subjects will receive a personal electronic diary at the trial site and will be instructed on how to use it.

The tablet computers will be kept at the trial site and subjects will be instructed on how to use it.

No queries will be issued to the investigator for these data, except for clarification of subject identifiers and any operational issues. No queries will be raised to the subject.

With database lock, the writing access to the electronic patient-reported outcome system will be removed. The investigator will receive all data captured for his or her subjects, in a human readable form, on read-only media for his or her files. The information will be provided to the investigator prior to system decommissioning.

13.3 External data

Trial data not recorded in the eCRF or subject-reported outcome, but requested per protocol (e.g., safety laboratory data, ECG data) will be collected and validated via sponsor internal or external data providers. The data integration into the clinical data and respective quality control measures are described in the Data Management Plan.

13.4 Data management

Data management will be performed by sponsor personnel or by authorized sponsor representatives. Documentation of the responsibilities and delegation thereof will be maintained in the trial master file.

All aspects of the data management process, including data validation and query management, medical coding, handling of external data, data lock procedures are described in the Data Management Plan. Details on data validation are described in the Data Validation Plan.

13.5 Source data

Source data is defined by GCP as “all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)”.

Source data comprise clinical documentation, data, and records (e.g., clinic/hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, and data and records arising from departments such as the pharmacy, laboratory, and medico-technical departments) that describe or record the methods, conduct, or results of the trial, the factors affecting the trial, and the actions taken.

All source data arising from the trial will be kept by the investigator, who must provide direct access for trial-related monitoring, audits, ethics committee review, and regulatory inspection.

In certain circumstances, data may only be recorded in the trial-specific eCRF and not in other documents. When this occurs, the eCRF is considered to be the source document. Data expected to be only recorded in the eCRF are race/ethnicity and sex.

The nature and location of all source data/clinical documentation will be identified and documented by the investigator to ensure that all sources of original data required to complete the eCRF are known to the sponsor and/or trial site personnel and are accessible for verification during trial-related monitoring, audits, relevant IEC/IRB review, and inspections.

For subject-reported outcomes captured directly via the electronic patient-reported outcome system, source data is defined as the data residing in the vendor’s database.

13.6 Investigator's site file and the trial master file

The principal investigator is responsible for the filing of all essential documents in an investigator's site file. The sponsor is responsible for the timely filing of all essential documents in the trial master file. As applicable, these files must be available at monitoring visits and during audits or regulatory inspections.

After trial completion, the principal investigator must ensure that all source data/documentation related to the trial is recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. The principal investigator must take measures to prevent accidental or premature destruction of these documents.

The principal investigator must keep the investigator's site file, the source data/documentation arising from the trial according to the prescribed record retention period in the country and/or according to the hospital policy, but at least until informed by the sponsor that the trial-related records are no longer required.

14 QUANTITATIVE ANALYSES

14.1 Statistical methods and sample size determination

14.1.1 Sample size rationale

The sample size rationale for the trial is provided in Section 1.5.1.

14.1.2 General description of statistical analyses

The statistical analysis of this trial will be planned, performed, and reported by sponsor personnel or by authorized sponsor delegates.

The data collected and derived for the trial will be presented in subject data listings.

Data collected in this trial will be summarized according to their nature as follows:

- Continuous variables: arithmetic mean, standard deviation, minimum and maximum values, median and quartiles depending on the number of observations.
- Categorical variables: absolute and relative frequencies.
- Time-to-event variables: Kaplan-Meier estimates together with the 95% confidence intervals and the hazard rate will be provided with the respective number at risk and the number censored at the relevant time points. In addition, the median time-to-event and its 95% confidence interval will be presented.

All the statistical analyses will be performed by treatment group (and overall where appropriate).

Sites will be pooled by geographic region. Geographic regions will be defined as USA/Canada, Europe, and Other Regions (including Asia-Pacific and Australia/New Zealand).

The trial will be analyzed once all the data is cleaned and the database is locked.

Full details of the planned statistical analyses will be described in the trial statistical analysis plan.

14.1.3 Analysis populations (analysis sets)

For the definition of analysis populations, please refer to Section [1.5.2](#).

14.1.4 Subject disposition

Subject disposition will be summarized descriptively for all enrolled subjects. Discontinuations will be summarized descriptively for all allocated subjects.

14.1.5 Analysis of demographic data and other baseline characteristics

Subject demographics and other baseline characteristics will be summarized descriptively by treatment group and overall for the Full Analysis Set and the Safety Set.

14.1.6 Concomitant medication and therapies

Concomitant medication and therapies will be summarized descriptively in the FAS and SAF with special focus on concomitant analgesic medication. Further summaries may be provided for specified therapies.

14.1.7 Analysis of efficacy data

All primary and secondary efficacy parameters will be summarized by descriptive statistics. The analysis of the primary efficacy endpoint will be performed on the Full Analysis Set. All other efficacy endpoints will be descriptively summarized in the Full Analysis Set. Confirmatory testing will be performed for the primary endpoint and for selected secondary endpoints. Further analyses may be done, including statistical hypothesis tests, but all analyses will be exploratory in nature and will not provide confirmatory evidence.

14.1.7.1 Analysis of the primary endpoint

See Section [1.2](#) for the definition of the primary endpoint.

14.1.7.1.1 Primary analysis

For the primary objective of the trial, the primary estimand is 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 will be estimated by the analysis of the primary efficacy endpoint for the Full Analysis Set. The primary analysis will fit an 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 will be 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 will be tabulated. This analysis will be performed using only the observed values without imputation of missing values.

A descriptive summary of the weekly averages and the changes from baseline will be generated by treatment group. Graphical displays will be used if appropriate.

14.1.7.1.2 Sensitivity analysis

Additional sensitivity analyses will be performed to assess the robustness of primary analysis results. Sensitivity analyses will include the imputation of missing pain intensity scores using different PMMs.

14.1.7.2 Analysis of the secondary efficacy endpoints

All secondary efficacy endpoints will be analyzed for the Full Analysis Set.

Average pain intensity

The change from baseline in the average pain intensity, recorded on the tablet computer, will be analyzed with an MMRM, including the covariate baseline pain intensity score, and the factors geographic region, week, treatment, and treatment-by-week interaction as fixed effects, and subject as random effect. An unstructured covariance matrix will be used to model the covariance structure.

The analysis will be performed using the contrast, i.e., the mixed model Wald test, of 400 mg neridronic acid versus placebo at Week 26 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 will be tabulated. This analysis will be performed using the observed values without imputation of missing values.

Pain response to treatment

Pain response to treatment, defined as an at least 30% decrease from baseline in average pain intensity, recorded on the tablet computer, will be derived. If a subject shows a worsening or the pain intensity score for the respective visit is missing then the subject will be considered a pain non-responder for the respective visit. A logistic regression model at Week 12 and Week 26 will be fitted to the data, including the covariate baseline pain intensity score, and the factors geographic region, and treatment as fixed effects. Model-based parameter estimates, standard errors, 95% confidence intervals, and p-values for the odds ratio at Week 12 and Week 26 between 400 mg neridronic acid and placebo will be tabulated.

The analysis of pain response to treatment will include a cumulative responder analysis at Week 12, Week 26, and Week 52, where responder rates will be calculated for different percentage thresholds for decrease from baseline in average pain intensity.

Dynamic mechanical allodynia

The change from baseline in the DMA will be analyzed using a similar model as for average pain intensity. Only subjects with allodynia at baseline, i.e., a DMA score greater than 0 on the 0 to 10 NRS, will be included in the analysis.

Pressure pain threshold

The change from baseline in the ratio of the PPT in the affected limb to the PPT in the unaffected limb for the thenar muscle/abductor hallucis muscle will be analyzed using a similar model as for average pain intensity. Only subjects with deep somatic pain (PPT ! 300 kPa) in the affected limb at baseline will be included in the analysis.

Edema

The change from baseline in edema will be analyzed using a similar model as for average pain intensity. Only subjects with presence of the CRPS sign “asymmetric edema” at baseline will be included in the analysis.

14.1.7.3 Handling of missing data

Diligent attempts will be made to limit the amount of missing data in the primary efficacy endpoint. Efforts will be made to follow-up subjects who discontinue treatment and to collect the primary efficacy endpoint for the statistical analysis.

The primary analysis using the MMRM is based on the MAR assumption. For the treatment policy or de facto estimand, the MAR assumption is justified for neridronic acid owing to the long half-life in bone and the anticipated persistent effect over the 12-week trial period. It can be assumed that the effect of neridronic acid continues after the treatment period is completed, and it also persists after the treatment period regardless of trial completion or early discontinuation. Therefore, the response of discontinued subjects will not change if the subjects continue to receive the stable therapy that they receive during the 12-week trial period up to Visit 8. If subjects change their treatment after discontinuation from the trial, it is nevertheless reasonable to assume that their response is not significantly altered as there are currently no established effective treatments. Hence, the MAR assumption is considered a plausible missingness mechanism for the primary estimand in the case of neridronic acid.

The MAR assumption cannot be verified based on data observed in the trial. Deviations from MAR cannot be excluded and several plausible MNAR assumptions will be investigated to assess their impact. MNAR assumptions will be defined via PMMs specifying the distribution of missing values, e.g., for subjects discontinuing before the end of the trial. Plausible PMMs for the primary estimand are PMI and the delta shift method.

Placebo multiple imputation is a reference-based approach based on the copy reference method. It models the means of missing values in the active arm based on the means observed in the placebo arm (reference arm). The method assumes that the response of discontinued subjects in the active arm gradually approaches the response in the placebo arm and eventually no effect of neridronic acid persists after a subject discontinues. For neridronic acid this appears conservative in light of the anticipated persistent effect.

The delta shift method models the means of missing values in the active arm by adding a pre-specified value Δ to the observed means in the active arm. The method includes a tipping point analysis, which is defined as the delta that must be added in order to overturn conclusions from the primary analysis from statistically significant to statistically insignificant. The method assumes that discontinued subjects in the active arm have higher pain compared to subjects who stay in the trial. Again this seems conservative if persistence of effect can be assumed for neridronic acid.

Overall, the 2 PMMs can be considered more conservative than MAR because they model missing pain intensity scores in the active arm using higher mean values than the means actually observed, whereas the placebo arm is not changed. In this way, neridronic acid is effectively penalized under these assumptions.

In summary, for neridronic acid the MAR assumption seems to be the most plausible missingness assumption for analyses estimating the primary estimand. It will be supplemented by sensitivity analyses based on MNAR assumptions representing plausible and reasonably conservative deviations from MAR.

14.1.7.4 Confirmatory testing strategy for secondary endpoints

A confirmatory testing procedure will be used for testing of the superiority of neridronic acid 400 mg versus placebo with respect to the primary and selected secondary efficacy endpoints (change from baseline to Week 26 in the average pain intensity, change from baseline to Week 12 in the pain intensity level of DMA, change from baseline to Week 12 in the PPT ratio, and change from baseline to Week 12 in the ratio of figure of eight measurements).

First, the primary endpoint will be tested at a one-sided level $\alpha = 2.5\%$. If the first test is statistically significant, the 4 secondary endpoints will be tested in a second stage.

To control for the family-wise type I error rate at the one-sided 2.5% level, a hybrid Hochberg-Hommel step-up procedure (hybrid-0 procedure in Gou et al. 2014) will be applied. The testing procedure uses the ordered p-values $p_{(1)} \geq p_{(2)} \geq p_{(3)} \geq p_{(4)}$. At first, if the largest p-value $p_{(1)} \leq \alpha$, then all 4 hypotheses are rejected. Otherwise the associated null hypothesis $H_{(1)}$ is accepted and testing proceeds to the next step. In general, at Step $i = 2, \dots, 4$, if $p_{(i)} \leq c_i \alpha$, then any hypothesis with p-value $\leq d_i \alpha$ will be rejected and testing stops; otherwise the null hypothesis $H_{(i)}$ and testing continues at the next step. At Step 4, the null hypothesis $H_{(4)}$ is rejected if $p_{(4)} \leq \alpha/4$; otherwise $H_{(4)}$ is accepted. The constants used in the testing procedure are defined by $c_i = (i+1)/(2i)$ and $d_i = 1/i$ and are given in the table below.

I	1	2	3	4
c_i	1	3/4	2/3	5/8
d_i	1	1/2	1/3	1/4

This semiparametric multiple testing procedure controls the family-wise error rate in the strong sense if the test statistics follow a multivariate normal distribution with non-negative correlation coefficients (Gou et al. 2014) which can be assumed for the investigated 4 efficacy endpoints.

14.1.7.5 Subgroup analyses

Subgroup analyses may be done if appropriate and will be specified in the statistical analysis plan.

14.1.8 Analysis of safety data

The analysis of safety data will be performed using the Safety Set.

14.1.8.1 Adverse events

A definition of adverse event is given in Section 12.4.1.

The original terms recorded in the eCRF to identify adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock.

Adverse events are only considered treatment emergent adverse events (TEAEs) if they start after first administration of IMP. All adverse events occurring in a subject administered a trial treatment and which do not necessarily have a causal relationship with this treatment will be defined as TEAEs. In addition, pre-treatment adverse events which worsen during the treatment periods are also considered TEAEs.

Treatment emergent adverse events will be summarized.

An overview of the number and percentage of subjects with at least 1 TEAE, serious TEAEs, non-serious TEAEs, unexpected TEAEs, related TEAEs, related serious TEAEs, TEAEs leading to discontinuation from IMP, TEAEs leading to discontinuation from the trial, and deaths will be created.

The number and percentage of subjects with adverse events and the number and percentage of events will be summarized by System Organ Class and Preferred Term for TEAEs, serious TEAEs, non-serious TEAEs, and related TEAEs.

Additional summaries by intensity, causal relationship, outcome, countermeasure, time to onset, duration, and expectedness will be provided.

Subjects with SAEs and subjects with adverse events leading to trial/treatment discontinuation will additionally be listed.

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

14.1.8.2 Safety laboratory values, vital signs, 12-lead ECG

Safety laboratory values, vital signs, and 12-lead ECG (including changes from baseline as applicable) will be descriptively summarized per visit.

Baseline will be the value collected on Day 1 (Visit 2) prior to first administration of IMP.

A listing of subjects with values outside the sponsor-defined alert ranges will be provided.

The ECG printouts will be interpreted by the investigator as “normal”, “abnormal, but clinically not relevant”, or “abnormal and clinically relevant”. Results from this interpretation will be reported in subject data listings.

14.1.9 Analysis of neridronic acid plasma concentration data

Pharmacokinetic concentrations will be analyzed in the Pharmacokinetic Set. Descriptive statistics and optionally graphs of the observed neridronic acid plasma concentrations at the planned time windows will be created. Owing to the sparse sampling and the random time points, no derivation and analysis of non-compartmental pharmacokinetic parameters is foreseen.

14.1.10 Analysis of pharmacodynamic data

Bone turnover marker values will be descriptively summarized by parameter for the Pharmacodynamic Set.

Baseline is defined by the value on Day 1 (Visit 2).

14.1.11 Analysis of health economics outcome and work productivity data

Health economics and work productivity data will be summarized descriptively for the Full Analysis Set.

14.1.12 Analysis of soluble interleukin-2 receptor

Analysis of sIL-2R concentrations will be summarized descriptively for the Safety Set.

14.1.13 Interim analysis

The interim analysis for the trial is described in Section [1.5.3.7](#).

14.2 Pharmacometric analyses

Modeling and simulation analyses will be performed by sponsor personnel or by authorized sponsor delegates.

A previously developed population pharmacokinetics model will be updated using the plasma concentrations-time data for neridronic acid.

An exploratory evaluation of the potential exposure-response relationships between neridronic acid exposure levels and the primary efficacy endpoint will be performed.

Based on the graphical exploration outcome, further investigations will be performed if deemed necessary.

Population pharmacokinetics and exposure-response modeling will be performed by means of a nonlinear mixed effect modeling approach as implemented in NONMEM[®].

Details will be described in pharmacometric analysis plans.

The results of any analyses will be reported in a pharmacometric report, i.e., separately from the integrated clinical trial report.

14.3 Analysis of the trial – pharmacogenetic and omics analysis

The pharmacogenetic testing will be performed on blood samples from this trial after the clinical data has been unblinded if a safety signal is seen, or a decision is made to analyze the relationship between single-nucleotide polymorphisms of genetically polymorphic genes and their corresponding proteins and pathways with pharmacokinetics or pharmacodynamics of the compound.

The objectives and methods of the pharmacogenetic testing will be described in a pharmacogenetic testing plan, which will be finalized before the pharmacogenetic testing starts. The genotyping study plan describing technical details of the pharmacogenetic testing will be provided by the genetic CRO. The results of the pharmacogenetic and omics testing will be reported by the CRO in a separate study report.

The pharmacogenetic data generated will not be used to make a diagnosis about the health of a subject.

The results of the pharmacogenetic and omics testing for individual trial subjects will not be supplied to the trial subject or to the subject's physician.

14.4 Ad hoc analyses

Data collected in this trial may be used for ad hoc medical or scientific analyses, e.g., analyses to explore pharmacokinetic/pharmacodynamic relationships. These analyses will be planned, performed, and reported by sponsor personnel or by authorized sponsor delegates in accordance with sponsor SOPs.

15 QUALITY SYSTEM, AUDIT, AND INSPECTION

15.1 Quality system

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs.

15.2 Data quality assurance

The accuracy and reliability of the trial data will be assured by careful CRO/investigator selection and oversight by the performance of a combination of trial site visits, training, monitoring visits, remote verification by the sponsor or appropriate use of electronic tools by the trial site, data cleaning, and audits.

Trial site monitoring as defined in GCP will be performed by sponsor personnel or by authorized sponsor delegates at pre-defined intervals depending on the progress of the trial.

Corrections, amendments, or clarifying statements resulting from monitoring visits should be made by the investigator where necessary.

Appropriate checking against source documents must be done by the sponsor.

Audits as defined by GCP should be performed for this trial. The auditors will be independent of the trial and its performance.

15.3 Inspections

The principal investigator, any investigator(s), the sponsor, or personnel at other establishments, must cooperate with any inspection of the documents, facilities, records, and other resources deemed appropriate by the inspecting authorities to be related to the trial and that may be located at the trial site, at the sponsor, or at other establishments.

The sponsor must be notified as soon as possible about any upcoming regulatory authority inspection.

16 GENERAL CONDITIONS AND AGREEMENTS

16.1 Insurance

If required by applicable regulatory requirements, the sponsor will arrange suitable insurance for the subjects included in this trial and provide the investigator with the relevant terms and conditions of this insurance. The investigator must inform all subjects about this insurance and (if requested) be prepared to explain the relevant terms and conditions of this insurance to the subject.

If changes to the trial are implemented after the initial insurance was arranged, e.g., due to protocol amendments, the sponsor will notify the insurance company of these changes in accordance with the insurance conditions. If changes to insurance arise, the sponsor will inform the investigators who will then inform their subjects about relevant changes.

16.2 Legal regulations

This trial will be carried out in compliance with any applicable regulatory requirements.

Before initiating the trial, if required by the applicable regulatory requirements, the sponsor or its authorized legal representative and/or the investigator will submit any required documents to the appropriate authorities for review, acceptance, and/or permission to begin the trial.

16.3 Contracts

Specific contracts between the relevant parties, i.e., between the investigator/other parties at the trial sites and the sponsor or its local offices or CRO or its affiliates authorized by the sponsor, will be used to set out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. This protocol and other documentation may serve as the basis of such contracts. In case of discrepancies with other contracts, the provisions of the protocol prevail.

In addition, responsibility for insurance or indemnity to cover any liability of the investigator that may arise directly or indirectly from the investigator's participation in the trial will be specified in a contract between the investigator and sponsor, if applicable.

16.4 Subject data and data protection

Subject trial data will be stored in a manner maintaining confidentiality in accordance with applicable regulatory requirements.

The investigator must ensure that any documents or data given to the sponsor or authorized sponsor representatives do not contain information that would affect the confidentiality of the subject's identity.

The investigator will obtain permission for direct access to original subject data from the subject as part of the written informed consent procedure (see Section 4.2). This gives permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor personnel or its representatives, and auditors) with direct access must take all reasonable precautions within the

constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the subject's identity and sponsor's proprietary information.

16.5 Public disclosure

The results of this trial will be publically disclosed in accordance with the sponsor's disclosure policy, the European Federation of Pharmaceutical Industries and Associations (EFPIA) Principles for Responsible Clinical Trial Data Sharing and applicable regulatory guidance (e.g., on ClinicalTrials.gov).

The results (or parts thereof) of this trial may be published as a publication (e.g., journal publication) or at a congress (e.g., as a poster or presentation). The sponsor reserves the right to review any proposed full publication or poster or presentation of the results of this trial by the coordinating or other investigator before they are submitted for publication or public disclosure.

Neither the sponsor nor the coordinating investigator has the right to prohibit publication or public disclosure. Publication or public disclosure can be postponed for patent purposes.

16.6 Trial results reporting

A final report integrating clinical, pharmacokinetic, pharmacodynamic, and statistical results will be prepared by the sponsor. The international coordinating investigator will approve the final report on behalf of the participating investigators.

The sponsor will provide the competent authority/ies and relevant IECs or IRBs with a summary of the trial results in accordance with applicable regulatory requirements.

All principal investigators will be provided with a summary of the trial results.

All entered subjects will be provided access to a summary of the trial results in a lay-understandable form.

16.7 Approval

16.7.1 Sponsor

This protocol has been approved in accordance with sponsor SOPs.

16.7.2 Coordinating investigator

This protocol has been approved by the international coordinating investigator.

17 REFERENCES

Investigator's brochure neridronic acid, current edition.

Abiogen Pharma S.p.A. Clinical Study Report NERI-AS001-07. A randomized, double-blind, placebo controlled study to assess the safety and the efficacy of neridronate 100 mg – 4 i.v. infusions in a course of 10 days treatment – in patients with algodystrophic syndrome. 22 July 2011.

Guidelines

European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical medicinal products intended for the treatment of neuropathic pain. CPMP/EWP/252/03 Rev. 1. 24 Jan 2007.

European Medicines Agency. Committee for medicinal Products for Human Use (CHMP) Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products. 12 Dec 2011.

Food and Drug Administration Guidance for Industry. Patient-reported outcome measures: use in medical product development to support labeling claims. Dec 2009.

ICH E10: Choice of control group in clinical trials. CPMP/ICH/364/96. Jan 2001.

ICH E15: Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories. Apr 2008.

United States Food and Drug Administration. Department of Health and Human Services. Guidance for Industry. Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling. Jan 2013.

Publications

Al Nofal AA, Altayar O, BenKhadra K, Qasim Agha OQ, Asi N, Nabhan M, et al. Bone turnover markers in Paget's disease of the bone: A Systematic review and meta-analysis. *Osteoporos Int* 2015; 26 (7): 1875-91.

Atkins RM, Yates AJ, Gray RE, Urwin GH, Hamdy NA, Beneton MN, et al. Amino hexane diphosphonate in the treatment of Paget's disease of bone. *J Bone Miner Res* 1987; 2 (4): 273-9.

Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* 2010; 9 (8): 807-19.

Bean DJ, Johnson MH, Heiss-Dunlop W, Kydd RR. Extent of recovery in the first 12 months of complex regional pain syndrome type-1: A prospective study. *Eur J Pain* 2016; 20 (6): 884-94.

Bharwani KD, Dirckx M, Stronks DL, Dik WA, Schreurs MWJ, Huygen FJPM. Elevated Plasma Levels of sIL-2R in Complex Regional Pain Syndrome: A Pathogenic Role for T-Lymphocytes? *Mediators Inflamm* 2017: 2764261.

Bruehl S. Complex regional pain syndrome. *BMJ* 2015; 351: h2730 doi:10.1136/bmj.h2730

Brunner F, Schmid A, Kissling R, Held U, Bachmann LM. Biphosphonates for the therapy of complex regional pain syndrome I – systematic review. *Eur J Pain* 2009; 13 (1): 17-21.

Carpenter JR, Kenward MG. Multiple Imputation and its Application. New York: Wiley; 2013. Choosing the number of imputations.

Cella D, Yount S, Rothrock N, Gershon R, Cook K, Reeve B, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap Cooperative Group during its first two years. *Med Care* 2007; 45 (5): S3-11.

Choi SW, Podrabsky T, McKinney N, Schalet BD, Cook KF, Cella D. PROSetta Stone® Analysis Report: a Rosetta Stone for Patient Reported Outcomes. 2012. Volume 1. Chicago, IL: Department

of Medical Social Sciences, Feinberg School of Medicine, Northwestern University. [accessed at <http://www.prosettastone.org>].

Cossins L, Okell RW, Cameron H, Simpson B, Poole HM, Goebel A. Treatment of complex regional pain syndrome in adults: a systematic review of randomized controlled trials published from June 2000 to February 2012. *Eur J Pain* 2013; 17 (2): 158-73.

de Rooij AM, de Mos M, Sturkenboom MC, Marinus J, van den Maagdenberg AM, van Hilten JJ. Familial occurrence of complex regional pain syndrome. *Eur J Pain* 2009; 13 (2): 171-7.

Dmitrienko A, Molenberghs G, Chuang-Stein C, Offen, W. Analysis of clinical trials using SAS®: a practical guide, Cary, NC: SAS Institute Inc.; 2005, p. 308 ff.

dos Reis FA, Alves Ribeiro E, de Tarso Camillo de Carvalho E, Guimarães Belchior AC, Coelho Arakaki J, et al. Analysis of the Figure-of-Eight method and volumetry reliability for ankle edema measurement. *Rev Bras Med Esporte* 2009; 10 (6): 472-4. (English version)

Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005; 113 (1-2): 9-19.

Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008; 9 (2): 105-21.

Dworkin RH, Turk DC, Revicki DA, Harding G, Coyne KS, Peirce-Sandner S, et al. Development and initial validation of an expanded and revised version of the Short-form McGill Pain Questionnaire (SF-MPQ-2). *Pain* 2009; 144 (1-2): 35-42.

Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; 94 (2): 149-58.

Gatti D, Rossini M, Viapiana O, Idolazzi L, Adami S. Clinical development of neridronate: potential for new applications. *Ther Clin Risk Manag* 2013; 9: 139-47.

Gatti D, Rossini M, Adami S. Management of patients with complex regional pain syndrome type I. *Osteoporos Int* 2016; 27 (8): 2423-31.

Goebel A. Management of adult patients with long-standing complex regional pain syndrome. *Pain Manag* 2013; 3 (2): 137-46.

Gou J, Tamhane, Xi D, Rom D. A class of improved hybrid Hochberg-Hommel type step-up multiple test procedures. *Biometrika* 2014; 101 (4): 899-911.

Grieve S, Perez RS, Birklein F, Brunner F, Bruehl S, Harden RN, et al. Recommendations for a first Core Outcome Measurement set for complex regional pain syndrome clinical studies. *Pain* 2017; 158 (6): 1083-90.

Harden RN, Bruehl S, Perez SG, Birklein F, Marinus J, Maihofner C, et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. *Pain* 2010a; 150 (2): 268-74.

-
- Harden RN, Bruehl S, Perez RS, Birklein F, Marinus J, Maihofner C, et al. Development of a severity score for CRPS. *Pain* 2010b; 151 (3): 870-6.
- Harden RN, Oaklander AL, Burton AW, Perez RS, Richardson K, Swan M, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th Edition. *Pain Med* 2013; 14 (2): 180-229.
- Jung K, Lein, M. Bone turnover markers in serum and urine as diagnostic, prognostic and monitoring biomarkers of bone metastasis. *Biochim Biophys Acta* 2014; 1846 (2): 425-38.
- Khosla S, Bilezikian JP, Dempster DW, Lewiecki EM, Miller PD, Neer RM, et al. Benefits and risks of bisphosphonate therapy for osteoporosis. *J Clin Endocrinol Metab* 2012; 97 (7): 2272-82.
- Little RJA and Rubin DB. Estimation of imputation uncertainty. In: *Statistical analysis with missing data*, 2nd ed. New York: Wiley; 2002.
- Leard JS, Breglio L, Fraga L, Ellrod N, Nadler L, Yasso M, et al. Reliability and concurrent validity of the figure-of-eight method of measuring hand size in patients with hand pathology. *J Orthop Sports Phys Ther* 2004; 34 (6): 335-40.
- Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150 (9): 604-12.
- Maier C, Baron R, Tölle TR, Binder A, Birbaumer N, Birklein F, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain* 2010; 150 (3): 439-50.
- Mainka T, Bischoff FS, Baron R, Krumova EK, Nicolas V, Pennekamp W, et al. Comparison of muscle and joint pressure-pain thresholds in patients with complex regional pain syndrome and upper limb pain of other origin. *Pain* 2014; 155 (3): 591-7.
- Maliepaard M, Nofziger C, Papaluca M, Zineh I, Uyama Y, Prasad K, et al. Pharmacogenetics in the evaluation of new drugs: a multiregional regulatory perspective. *Nat Rev Drug Disc* 2013; 12 (2): 103-15.
- McCloskey EV, Yates AJ, Beneton MN, Galloway J, Harris S, Kanis JA. Comparative effects of intravenous diphosphonates on calcium and skeletal metabolism in man. *Bone* 1987; 8 (Suppl 1): S35-41.
- Naylor K, Eastell R. Bone turnover markers: use in osteoporosis. *Nat Rev Rheumatol* 2012; 8 (7): 379-89.
- Nicholas MK. The pain self-efficacy questionnaire: Taking pain into account. *Eur J Pain* 2007; 11 (2): 153-63.
- O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome. *Cochrane Database Syst Rev* 2013; 4: CD009416.
- Oaklander AL, Horowitz SH. The complex regional pain syndrome. *Handb Clin Neurol* 2015; 131: 481-503.

-
- Oerlemans HM, Goris RJ, Oostendorp RA. Impairment level sumscore in reflex sympathetic dystrophy of one upper extremity. *Arch Phys Med Rehabil* 1998; 79 (8): 979-90.
- Pellecchia GL. Figure-of-eight method of measuring hand size: reliability and concurrent validity. *J Hand Ther* 2003; 16 (4): 300-4.
- Perez RS, Oerlemans HM, Zuurmond WW, De Lange JJ. Impairment level SumScore for lower extremity Complex Regional Pain Syndrome type I. *Disabil Rehabil* 2003; 25 (17): 984-91.
- Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D on behalf of the PROMIS Cooperative Group. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS®): depression, anxiety, and anger. *Assessment* 2011; 18 (3): 263-83.
- Polyzos SA, Anastasilakis AD, Makras P, Terpos E. Paget's disease of bone and calcium homeostasis: focus on bisphosphonate treatment. *Exp Clin Endocrinol Diabetes* 2011; 119 (9): 519-24.
- Reid IR, Gamble GD, Mesenbrink P, Lakatos P, Black DM. Characterization of and risk factors for the acute-phase response after zoledronic acid. *J Clin Endocrinol Metab* 2010; 95 (9): 4380-7.
- Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993; 4 (5): 353-65.
- Rolke R, Andrews K., Magerl W, Treede R-D. Investigator's Brochure. A standardized battery of Quantitative Sensory Testing according to the protocol of the German Research Network on Neuropathic Pain (DFNS), v2.1, 2010. Accessed at http://www.neuro.med.tumuenchen.de/dfns/pdfs/QST-Investigators_brochure_Version_2_1_final_english_2010_07_09.pdf.
- Rosen CJ, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, et al. IOM committee members respond to Endocrine Society vitamin D guideline. *J Clin Endocrinol Metab* 2012; 97 (4): 1146-52.
- Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* 2011; 96 (1): 53-8.
- Sayyad A, Graciosa JR, Osborne M, Kuroda MM, Jacobs G, Harden RN. Poster 314. Complex regional pain syndrome severity score: development of a clinical tool for monitoring disease evolution. *PM&R* 2011; 3 (10): S281.
- Silverman SL, Kriegman A, Goncalves J, Kianifard F, Carlson T, Leary E. Effect of acetaminophen and fluvastatin on post-dose symptoms following infusion of zoledronic acid. *Osteoporos Int* 2011; 22 (8): 2337-45.
- Stone AA, Broderick JE, Shiffman SS, Schwartz JE. Understanding recall of weekly pain from a momentary assessment perspective: absolute agreement, between- and within-person consistency, and judged change in weekly pain. *Pain* 2004; 107 (1-2): 61-9.
- Sullivan ML, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment* 1995; 7 (4): 524-32.

Sullivan M, Tanzer M, Stanish W, Fallaha M, Keefe FJ, Simmonds M, et al. Psychological determinants of problematic outcomes following Total Knee Arthroplasty. *Pain* 2009; 143 (1-2): 123-9.

Varenna M, Zucchi F, Ghiringhelli D, Binelli L, Bevilacqua M, Bettica P, et al. Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double-blind, placebo controlled study. *J Rheumatol* 2000; 27 (6): 1477-83.

Varenna M, Casari S, Zucchi F, Binelli L, Sinigaglia L. Neridronato endovenoso nel trattamento della sindrome algodistrofica. Abstract presented at 4th National Congress of Italian Society of Osteoporosis, Mineral Metabolism and Skeletal Diseases. 2004. [Abstract translated from Italian]

Varenna M, Adami S, Rossini M, Gatti D, Idolazzi L, Zucchi F, et al. Treatment of complex regional pain syndrome type I with neridronate: a randomized, double-blind, placebo-controlled study. *Rheumatology* 2013; 52 (3): 534-42.

Vasikaran S, Eastell R, Bruyère O, Foldes AJ, Garnero P, Griesmacher A, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int* 2011; 22 (2): 391-420.

Verbeke G, Molenberghs G. Linear mixed models for longitudinal data. Springer Series in Statistics. 2009. p.209 ff.

Wertli MM, Kessels AG, Perez RS, Bachmann LM, Brunner F. Rational pain management in complex regional pain syndrome 1 (CRPS 1)--a network meta-analysis. *Pain Med* 2014; 15 (9): 1575-89.

Wheater G, Elshahaly M, Tuck SP, Datta HK, van Laar JM. The clinical utility of bone marker measurements in osteoporosis. *J Transl Med* 2013; 11: 201.

Yalcin I, Bump RC. Validation of two global impression questionnaires for incontinence. *Am J Obstet Gynecol* 2003; 189 (1): 98-101.

Ziegler EA, Magerl W, Meyer RA, Treede RD. Secondary hyperalgesia to punctate mechanical stimuli. Central sensitization to A-fibre nociceptor input. *Brain* 1999; 122: 2245-57.

18 APPENDIX**18.1 List of potentially important medical concepts – classified by System Organ Class**

Blood and lymphatic system disorders		
Agranulocytosis	Aplastic anaemia	Blast cell proliferation (myeloproliferative and lymphoproliferative disorders)
Bone marrow depression	Disseminated intravascular coagulation (DIC)	Haemolytic anaemia
Histiocytosis	Loss of anticoagulation control	Pancytopenia
Splenic haemorrhage, infarction or thrombosis	Thrombocytopenia (<30000)	Thrombotic thrombocytopenic purpura
Cardiac disorders		
Angina unstable	Atrial flutter	Atrioventricular block complete
Cardiac arrest	Cardiac failure acute	Cardiac fibrillation
Cardiac tamponade	Cardiogenic shock	Cardiomyopathy acute
Coronary artery spasm	Cor pulmonale decompensated	Myocardial infarction
Torsade de pointes	Ventricular fibrillation	Ventricular tachycardia
Ear and labyrinth disorders		
Deafness	Vestibular ataxia	
Endocrine disorders		
Adrenocortical insufficiency acute		
Eye disorders		
Cataract/lens opacity	Glaucoma	Keratitis/corneal opacification
Macular degeneration	Optic neuropathy, atrophy	Papilloedema
Ptosis	Retinal artery/vein occlusion	Retinitis
Scotoma	Sudden visual loss	Uveitis
Vitreous detachment		
Gastrointestinal disorders		
Colitis haemorrhagic	Gastric ulcer haemorrhage	Gastric ulcer perforation
Haematemesis	Haemoperitoneum	Ileus
Intestinal ischaemia	Intestinal perforation	Melaena
Mesenteric occlusion	Mesenteric vein thrombosis	Pancreatitis
Peritonitis		
General disorders and administration site conditions		
Malignant hyperthermia		

Hepatobiliary disorders		
Hepatic failure	Hepatitis fulminant	Hepatic necrosis
Hepatorenal syndrome	Portal hypertension	Reye's syndrome
Immune system disorders		
Amyloidosis	Anaphylactic reaction	Anaphylactic shock
Graft versus host disease		
Infections and infestations		
Endotoxic shock	Sepsis	Toxic shock syndrome
Transmission of an infectious agent via a medicinal product		
Injury, poisoning and procedural complications		
Transplant failure	Wound dehiscence	
Metabolism and nutrition disorders		
Diabetic coma	Failure to thrive	Hypercalcaemia (CTC IV)
Hyperkalaemia (CTC IV)	Hypocalcaemia (CTC IV)	Hypokalaemia (CTC IV)
Lactic acidosis	Porphyria	Shock hypoglycaemic
Tetany		
Musculoskeletal and connective tissue disorders		
Aseptic necrosis bone	Fracture pathological	Muscle necrosis
Osteomalacia	Rhabdomyolysis	Systemic lupus erythematosus
Systemic sclerosis		
Nervous system disorders		
Amnesia	Anticholinergic syndrome	Aphasia
Cerebral oedema	Chorea	Coma
Convulsions	Demyelination	Encephalitis
Encephalopathy	Epilepsy	Guillain-Barré syndrome
Hydrocephalus	Intracranial haemorrhage	Meningitis
Multiple sclerosis	Myasthenia gravis	Myelitis
Neuroleptic malignant syndrome	Opisthotonus	Paralysis
Paresis	Parkinson's syndrome	Serotonin syndrome
Stroke	Tunnel vision	
Pregnancy, puerperium and perinatal conditions		
Abortion	Eclampsia	Intra-uterine death
Psychiatric disorders		
Anorexia nervosa	Delirium	Drug abuse
Drug dependence	Homicidal ideation	Intentional misuse
Self-injurious ideation/attempt	Suicidal ideation/attempt	Suicide completed

Renal and urinary disorders

Anuria	Goodpasture's syndrome	Haemolytic uraemic syndrome
Nephritis/nephritic syndrome	Nephrotic syndrome	Oliguria
Renal failure acute	Renal tubular necrosis	Urinary obstruction/retention

Reproductive system and breast disorders

Metrorrhagia/uterine haemorrhage	Priapism
----------------------------------	----------

Respiratory, thoracic and mediastinal disorders

Acute respiratory failure	Adult respiratory distress syndrome	Alveolitis allergic
Asphyxia	Bronchospasm	Laryngeal oedema
Pulmonary fibrosis	Pulmonary haemorrhage	Pulmonary infarction
Pulmonary vasculitis	Respiratory arrest	Status asthmaticus
Pulmonary oedema		

Skin and subcutaneous tissue disorders

Angioneurotic oedema	Erythema nodosum	Pemphigus
Stevens-Johnson syndrome	Toxic epidermal necrolysis	Vascular purpura

Vascular disorders

Acute circulatory failure	Embolism	Malignant hypertension
Necrosis ischaemic	Thrombosis	

Status: Dec 2017

CTC = Common Toxicity Criteria also referred to as the Common Terminology Criteria for Adverse Events (CTCAE).

18.2 Algorithm for follow-up investigation of potential or suspected cases of drug-induced liver injury

If alanine aminotransferase or aspartate aminotransferase is >3 x the upper limit of normal, repeat the lab test within 48 hours to 72 hours. The test should be performed for aspartate aminotransferase, alanine aminotransferase, creatine kinase, total, direct and indirect bilirubin, alkaline phosphatase, lipase and gamma glutamyl transferase.

If alanine aminotransferase or aspartate aminotransferase is >3 x the upper limit of normal, (confirmed by retesting), and total bilirubin is ≥ 2 x the upper limit of normal, the investigator and the sponsor should discuss the following recommendations:

- Initiate a close observation of the subject/patient.
- Repeat testing of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total, direct and indirect bilirubin, creatine kinase, gamma glutamyl transferase, international normalized ratio, eosinophilic granulocytes and lipase 2 times to 3 times weekly.
- Decrease the frequency of retesting to once a week or less if abnormalities stabilize or if the IMP has been discontinued.

If aspartate aminotransferase or alanine aminotransferase is >3 x the upper limit of normal and total bilirubin is >2 x the upper limit of normal, the investigator and the sponsor should discuss following recommendations:

- Repeat testing of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total, direct and indirect bilirubin, creatine kinase, gamma glutamyl transferase, international normalized ratio, eosinophilic granulocytes and lipase.
- Consult a hepatologist/gastroenterologist who must then conduct an obligatory abdominal ultrasound and other examinations (e.g., liver biopsy) as necessary.
- Obtain more detailed history of symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [$>5\%$]).
- Obtain history of concomitant medications, including herbal drugs, alcohol use or other drugs of abuse.
- As appropriate, conduct laboratory investigations for other possible causes of liver injury. Testing can be discussed with the sponsor.

18.3 Subject-reported outcomes

The subject-reported outcomes provided in the following sections are validated English samples.

18.3.1 Patient Global Impression of Change

DMS version: 1.0

ID: 1029120

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Since the start of the study, my overall status is:

✓ *one box only:*

- [1] Very Much Improved
- [2] Much Improved
- [3] Minimally Improved
- [4] No Change
- [5] Minimally Worse
- [6] Much Worse
- [7] Very Much Worse

(US/English)

18.3.2 Patient Global Impression of Severity

Please choose the response below that best describes the severity of your CRPS symptoms over the past week:

- ~ None
- ~ Mild
- ~ Moderate
- ~ Severe
- ~ Very severe

18.3.3 EuroQol-5 dimension-5 level

DMS version: 1.0

ID: 1028200



Health Questionnaire

English version for the UK

DMS version: 1.0

ID: 1028200

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

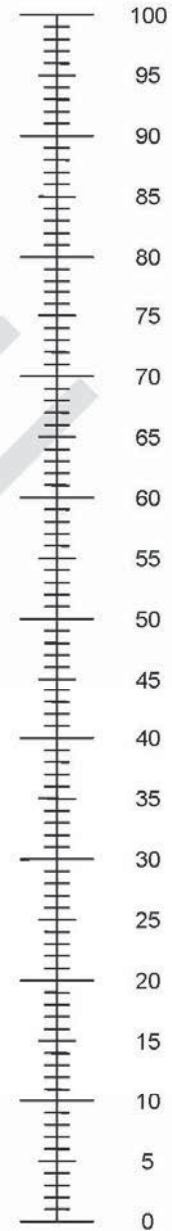
DMS version: 1.0

ID: 1028200

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine

18.3.4 PROMIS-29 profile version 2.0

PROMIS-29 Profile v2.0

Please respond to each question or statement by marking one box per row.

Physical Function		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA11 1	Are you able to do chores such as vacuuming or yard work?.....	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA21 2	Are you able to go up and down stairs at a normal pace?.....	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA28 3	Are you able to go for a walk of at least 15 minutes?.....	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA53 4	Are you able to run errands and shop?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Anxiety		Never	Rarely	Sometimes	Often	Always
EDANX01 5	I felt fearful.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDANX40 6	I found it hard to focus on anything other than my anxiety	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDANX41 7	My worries overwhelmed me.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDANX53 8	I felt uneasy	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Depression		Never	Rarely	Sometimes	Often	Always
EDDEP04 9	I felt worthless	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDDEP06 10	I felt helpless.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDDEP29 11	I felt depressed.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDDEP41 12	I felt hopeless.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Fatigue		Not at all	A little bit	Somewhat	Quite a bit	Very much
H17 13	I feel fatigued	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
AN3 14	I have trouble starting things because I am tired.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

PROMIS–29 Profile v2.0

Fatigue

In the past 7 days...

		Not at all	A little bit	Somewhat	Quite a bit	Very much
FATEXP41 15	How run-down did you feel on average? ...	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
FATEXP40 16	How fatigued were you on average?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Sleep Disturbance

In the past 7 days...

		Very poor	Poor	Fair	Good	Very good
Sleep109 17	My sleep quality was.....	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1

In the past 7 days...

		Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep116 18	My sleep was refreshing.....	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Sleep20 19	I had a problem with my sleep	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Sleep44 20	I had difficulty falling asleep	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Ability to Participate in Social Roles and Activities

		Never	Rarely	Sometimes	Usually	Always
SRPPER11 _CaPS 21	I have trouble doing all of my regular leisure activities with others.....	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
SRPPER18 _CaPS 22	I have trouble doing all of the family activities that I want to do	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
SRPPER23 _CaPS 23	I have trouble doing all of my usual work (include work at home)	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
SRPPER46 _CaPS 24	I have trouble doing all of the activities with friends that I want to do	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1

Pain Interference

In the past 7 days...

		Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ9 25	How much did pain interfere with your day to day activities?.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PAININ22 26	How much did pain interfere with work around the home?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PAININ31 27	How much did pain interfere with your ability to participate in social activities?.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PAININ34 28	How much did pain interfere with your household chores?.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

PROMIS–29 Profile v2.0

Pain Intensity

In the past 7 days...

Global07 29	How would you rate your pain on average?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		0	1	2	3	4	5	6	7	8	9	10
		No pain										Worst imaginable pain

18.3.5 PROMIS-EDDEP39

Item ID	Item Context	Item Stem	Responses
EDDEP39	In the past 7 days...	I felt I had no reason for living	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always

18.3.6 Short-form McGill Pain Questionnaire 2: 6 neuropathic pain items**Short-form McGill Pain Questionnaire 2 (SF-MPQ-2)**

For this questionnaire, I will provide you a list of words that describe some of the different qualities of pain and related symptoms. Please rate the intensity of each of the pain and related symptoms you felt during the past week on 0 to 10 scale, with 0 being no pain and 10 being the worst pain you can imagine. Use 0 if the word does not describe your pain or related symptoms. Limit yourself to a description of the pain related to your complex regional pain syndrome (CRPS) pain.

Hot burning pain	none	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	worst possible
0	1	2	3	4	5	6	7	8	9	10				
Cold-freezing pain	none	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	worst possible
0	1	2	3	4	5	6	7	8	9	10				
Pain caused by light touch	none	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	worst possible
0	1	2	3	4	5	6	7	8	9	10				
Itching	none	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	worst possible
0	1	2	3	4	5	6	7	8	9	10				
Tingling or 'pins and needles'	none	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	worst possible
0	1	2	3	4	5	6	7	8	9	10				
Numbness	none	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	worst possible
0	1	2	3	4	5	6	7	8	9	10				

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Items taken from the SF-MPQ-2 - United States/English - Mapi.

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SF-MPQ-2-6items_TS1.0_eng-USon.docx

18.3.7 Pain Catastrophizing Scale

Copyright © 1995
Michael J. Sullivan**PCS**

Client No.: _____ Age: _____ Sex: M() F() Date: _____

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all 1 – to a slight degree 2 – to a moderate degree 3 – to a great degree 4 – all the time

When I'm in pain ...

- 1 I worry all the time about whether the pain will end.
- 2 I feel I can't go on.
- 3 It's terrible and I think it's never going to get any better.
- 4 It's awful and I feel that it overwhelms me.
- 5 I feel I can't stand it anymore.
- 6 I become afraid that the pain will get worse.
- 7 I keep thinking of other painful events.
- 8 I anxiously want the pain to go away.
- 9 I can't seem to keep it out of my mind.
- 10 I keep thinking about how much it hurts.
- 11 I keep thinking about how badly I want the pain to stop.
- 12 There's nothing I can do to reduce the intensity of the pain.
- 13 I wonder whether something serious may happen.

... Total

18.3.8 Pain Self Efficacy Questionnaire

PAIN SELF EFFICACY QUESTIONNAIRE (PSEQ)

M.K.Nicholas (1989)

NAME: _____ DATE: _____

Please rate how **confident** you are that you can do the following things at present, **despite the pain**. To indicate your answer circle **one** of the numbers on the scale under each item, where 0 = not at all confident and 6 = completely confident.

For example:

0	1	2	3	4	5	6
Not at all Confident						Completely confident

Remember, this questionnaire is **not** asking whether or not you have been doing these things, but rather **how confident you are that you can do them at present, despite the pain**.

1. I can enjoy things, despite the pain.

0	1	2	3	4	5	6
Not at all Confident						Completely confident

2. I can do most of the household chores (e.g. tidying-up, washing dishes, etc.), despite the pain.

0	1	2	3	4	5	6
Not at all Confident						Completely confident

3. I can socialise with my friends or family members as often as I used to do, despite the pain.

0	1	2	3	4	5	6
Not at all Confident						Completely confident

4. I can cope with my pain in most situations.

0	1	2	3	4	5	6
Not at all Confident						Completely confident

Turn over

5. I can do some form of work, despite the pain. ("work" includes housework, paid and unpaid work).

0 1 2 3 4 5 6
Not at all Completely
Confident confident

6. I can still do many of the things I enjoy doing, such as hobbies or leisure activity, despite pain.

0 1 2 3 4 5 6
Not at all Completely
Confident confident

7. I can cope with my pain without medication.

0 1 2 3 4 5 6
Not at all Completely
Confident confident

8. I can still accomplish most of my goals in life, despite the pain.

0 1 2 3 4 5 6
Not at all Completely
Confident confident

9. I can live a normal lifestyle, despite the pain.

0 1 2 3 4 5 6
Not at all Completely
Confident confident

10. I can gradually become more active, despite the pain.

0 1 2 3 4 5 6
Not at all Completely
Confident confident

18.3.9 Work Productivity and Activity Impairment Questionnaire: CRPS

**WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE:
COMPLEX REGIONAL PAIN SYNDROME VERSION (WPAI:CRPS)**

The following questions ask about the effect of your **CRPS** on your ability to work and perform regular daily activities. *Please fill in the blanks or circle a number, as indicated.*

- 1) Are you currently employed (working for pay)? ____ NO ____ YES
(If NO, check "NO" and skip to question 6)

The next questions refer to the **past seven days**, not including today.

- 2) During the past seven days, how many hours did you miss from work because of problems associated with your CRPS? *Include hours you missed on sick days, times you went in late, left early, etc., because of problems associated with CRPS. Do not include time you missed to participate in this study.*
____ HOURS

- 3) During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
____ HOURS

- 4) During the past seven days, how many hours did you actually work?
____ HOURS (If "0", skip to question 6)

- 5) During the past seven days, how much did **CRPS** affect your productivity while you were working? *Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If CRPS affected your work only a little, choose a low number. Choose a high number if CRPS affected your work a great deal.*

Consider only how much CRPS affected productivity while you were working.

CRPS had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	CRPS completely prevented me from working
---	------------------------	---

CIRCLE A NUMBER

- 6) During the past seven days, how much did **CRPS** affect your ability to do your regular daily activities, other than work at a job? *By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If CRPS affected your activities only a little, choose a low number. Choose a high number if CRPS affected your activities a great deal.*

Consider only how much CRPS affected your ability to do your regular daily activities, other than work at a job.

CRPS had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	CRPS completely prevented me from doing my daily activities
---	------------------------	---

CIRCLE A NUMBER

WPAI_CRPS (English - US)

18.4 Signs and symptoms of CRPS

Site # / Subject ID
_____/_____Date (MM/DD/YY)
____/____/____Visit 1 or Visit 2 **CRPS SEVERITY SCORE
DATABASE FORM**DIAGNOSIS: CRPS-I CRPS-II Non-CRPS: _____ETIOLOGY: Crush Surgery Fracture Laceration Other: _____DATE INJURY: ____/____/____ DATE SX ONSET: ____/____/____ LOCATION: L R UE LE

Current Numeric pain Rating Scale (NRS) of affected side: ____/10; 24 hr worst ____/10; 24hr best ____/10

SYMPTOMS

Comments:

Circle "Yes" or "No" for each as reported by patient over the **past 48 hours**:

YES	NO	Continuing, disproportionate pain ¹	_____
YES	NO	Allodynia, and/or Hyperalgesia ² : <i>specify</i> : <input type="checkbox"/> Allo <input type="checkbox"/> Hyper	_____
YES	NO	Temperature asymmetry ³ <i>If yes, specify</i> : <input type="checkbox"/> Cold <input type="checkbox"/> Warm <input type="checkbox"/> Labile	_____
YES	NO	Color asymmetry ⁴ <i>If yes, specify</i> : <input type="checkbox"/> Red <input type="checkbox"/> Blue <input type="checkbox"/> Other	_____
YES	NO	Sweating asymmetry ⁵	_____
YES	NO	Edema ⁶	_____
YES	NO	Dystrophic changes ⁷ <i>If yes, specify</i> : <input type="checkbox"/> Nails <input type="checkbox"/> Hair <input type="checkbox"/> Skin	_____
YES	NO	Motor abnormalities ⁸ <i>If yes, specify</i> : <input type="checkbox"/> Weak <input type="checkbox"/> Tremor <input type="checkbox"/> Dystonia	_____
		<input type="checkbox"/> Decreased ROM <input type="checkbox"/> Myoclonus	_____

SIGNS (as observed by examiner **this date**). Note any detailed comments on back:

YES	NO	Hyperalgesia to single pinprick ⁹	
YES	NO	Allodynia ¹⁰ <i>If yes, specify to</i> : <input type="checkbox"/> Light Touch <input type="checkbox"/> Deep Joint Pressure <input type="checkbox"/> Vibration <input type="checkbox"/> Cold <input type="checkbox"/> Heat	
YES	NO	Temperature asymmetry by palpation ¹¹ <i>If yes, specify</i> : <input type="checkbox"/> Affected Side Cooler <input type="checkbox"/> Affected Side Warmer	
YES	NO	Color asymmetry ¹² <i>If yes, specify</i> : Affected side: <input type="checkbox"/> Red <input type="checkbox"/> Blue or Pale <input type="checkbox"/> Mottled <input type="checkbox"/> Scar	
YES	NO	Asymmetric Edema ¹³ Notes: _____	
YES	NO	Sweating asymmetry ¹⁴ <i>If yes, specify</i> : <input type="checkbox"/> Increased on Affected Side <input type="checkbox"/> Decreased on Affected Side	
YES	NO	Dystrophic changes ¹⁵ <i>If yes, specify</i> : <input type="checkbox"/> Nails <input type="checkbox"/> Hair <input type="checkbox"/> Skin. Notes: _____	
YES	NO	Motor abnormalities ¹⁶ <i>If yes, specify</i> : <input type="checkbox"/> Tremor <input type="checkbox"/> Dystonia <input type="checkbox"/> Decreased Active ROM	
		<input type="checkbox"/> Weakness ____/5 (Rate 0-5 of most affected joint)	

18.5 Health Economics Outcome Questionnaire (sample)

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**Health Economics Outcome Questionnaire
Booklet
KF7013-02**Subject No.

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Subject No.

Emergency Room (ER) Visit

2. During the past 12 weeks, did you receive care in an emergency room without being admitted to the hospital?

- Yes No [SKIP to 3] Don't know

2.a. If Yes, how many times in the past 12 weeks? (#)

2.b. Please list the reason and date for each emergency room visit:

#	Major Reason for ER Visit	Date
1		 / / <small>DD MMM YYYY</small>
2		 / / <small>DD MMM YYYY</small>
3		 / / <small>DD MMM YYYY</small>

Nursing Home (NH) Stay

3. During the past 12 weeks, did you spend any nights in a nursing home for any reason (physical or emotional)?


- Yes No [SKIP to 4] Don't know

3.a. If Yes, how many times in the past 12 weeks? (#)

3.b. Please list reason, number of nights, and admission date for each nursing home stay:

#	Major Diagnosis or Reason for NH Stay	# of Nights	Admission Date
1			 / / <small>DD MMM YYYY</small>
2			 / / <small>DD MMM YYYY</small>
3			 / / <small>DD MMM YYYY</small>

Note: Keep the original completed form in the subject file. Transcribe the data to the eCRF. Assure consistency of the data related to reported medical history and adverse events for the subject.
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Subject No.

#	Provider Type	Used?	# visits in past 12 weeks	# phone calls in past 12 weeks	Major Diagnosis or Reason for Visit/Call
i	Integrated medicine	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
j	Chiropractor	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
k	Physical therapist	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
l	Occupational therapist	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
m	Visiting nurse	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
n	Home health aide	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
o	Other specialty (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
p	Other specialty (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
q	Other specialty (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			

Note: Keep the original completed form in the subject file. Transcribe the data to the eCRF. Assure consistency of the data related to reported medical history and adverse events for the subject.
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Subject No. | | | | | | | | | |

**HOME SERVICES, HOME HELP, FORMAL AND INFORMAL CAREGIVING,
DEVICES**

Home Services and Help

5. Which of the following types of services or help have you used in the past 12 weeks due to your CRPS-related pain?

#	Program/Service Type	Used?	# times in past 12 weeks	Average duration per time (min)
a	Cleaning or homemaking services	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know		
b	Meals delivered	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know		
c	Formal childcare / babysitting assistance	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know		
d	Transportation to help complete daily errands (e.g., shopping, bank, work, medical visits, pharmacy)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know		
e	Formal and informal caregiving	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know		

Special Product / Device / Tool

6. Did you use any special equipment/assistive tools the past 12 weeks due to your CRPS-related pain?

Special product / device / tool	Used?	#	Name of device/product/tool
Special equipment /assistive tools	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know	1	
		2	
		3	
		4	
		5	
		6	

Note: Keep the original completed form in the subject file. Transcribe the data to the eCRF. Assure consistency of the data related to reported medical history and adverse events for the subject.
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Subject No. | | | | | | | | | |

**HOME SERVICES, HOME HELP, FORMAL AND INFORMAL CAREGIVING,
DEVICES**

Home Services and Help

5. Which of the following types of services or help have you used in the past 12 weeks due to your CRPS-related pain?

#	Program/Service Type	Used?	# times in past 12 weeks	Average duration per time (min)
a	Cleaning or homemaking services	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know		
b	Meals delivered	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know		
c	Formal childcare / babysitting assistance	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know		
d	Transportation to help complete daily errands (e.g., shopping, bank, work, medical visits, pharmacy)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know		
e	Formal and informal caregiving	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know		

Special Product / Device / Tool

6. Did you use any special equipment/assistive tools the past 12 weeks due to your CRPS-related pain?

Special product / device / tool	Used?	#	Name of device/product/tool
Special equipment /assistive tools	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know	1	
		2	
		3	
		4	
		5	
		6	

Note: Keep the original completed form in the subject file. Transcribe the data to the eCRF. Assure consistency of the data related to reported medical history and adverse events for the subject.
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Subject No.

#	Provider Type	Used?	# visits in past 12 weeks	# phone calls in past 12 weeks	Major Diagnosis or Reason for Visit/Call
i	Integrated medicine	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
j	Chiropractor	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
k	Physical therapist	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
l	Occupational therapist	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
m	Visiting nurse	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
n	Home health aide	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
o	Other specialty (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
p	Other specialty (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			
q	Other specialty (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know			

Note: Keep the original completed form in the subject file. Transcribe the data to the eCRF. Assure consistency of the data related to reported medical history and adverse events for the subject.
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19 PROTOCOL AMENDMENTS

19.1 Protocol Amendment 01

Amendment rationale

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 have been implemented:

- Addition of weekly pain intensity assessments after Week 12 using an electronic diary.
- Clarification of concomitant analgesic medication use as a (non-objective related) outcome.
- Simplification of the description of “other data to be collected that are not directly attributed to or considered as an endpoint” (there was no change to the planned assessments or evaluations).
- Removal of specification of male contraception in inclusion criterion 6.
- Clarification in exclusion criterion 1 that the quoted eGFR and ACR thresholds refer to severe renal impairment.

Minor inconsistencies have also been corrected.

Detailed description of changes

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

In the table below, deleted text is crossed out and new text is highlighted using italics.

Changes to this protocol include:	
Formerly read:	Now reads:
Section 1.2: Trial objectives, endpoints, and outcomes Section 1.5.3: Statistical methods and analysis	
[...] All efficacy and safety endpoints evaluated during Treatment Period B and Follow-up Period 2...	[...] All efficacy and safety <i>data</i> evaluated during Treatment Period B and Follow-up Period 2...
Section 1.2: Trial objectives, endpoints, and outcomes	
<p><i>To assess the efficacy of neridronic acid in subjects with CRPS</i></p> <ul style="list-style-type: none"> • Change from baseline to Week 52 in average pain intensity recorded on the tablet computer. • Change from Week 26 to Week 52 in average pain intensity recorded on the tablet computer. • Pain response to treatment, defined as at least 50% decrease from baseline in the average pain intensity at Week 52, based on pain intensity recordings on the tablet computer. • Pain response to treatment, defined as at least 50% decrease from Week 26 in the average pain intensity at Week 52, based on pain 	<p><i>All efficacy assessments will be evaluated for the time points indicated in the schedules of events.</i></p> <p><i>To assess the efficacy of neridronic acid in subjects with CRPS</i></p> <ul style="list-style-type: none"> • Change from baseline in average pain intensity recorded on the tablet computer. • Change from Week 26 in average pain intensity recorded on the tablet computer. • Pain response to treatment, defined as at least 50% decrease from baseline in the average pain intensity, based on pain intensity recordings on the tablet computer. • Pain response to treatment, defined as at least 50% decrease from Week 26 in the average

Changes to this protocol include:	
Formerly read:	Now reads:
<p>intensity recordings on the tablet computer.</p> <ul style="list-style-type: none"> • Pain response to treatment, defined as at least 50% decrease from baseline in the average pain intensity at Week 12, based on pain intensity recordings on the tablet computer. • Pain response to treatment, defined as at least 50% decrease from baseline in the average pain intensity at Week 26, based on pain intensity recordings on the tablet computer. • Pain response to treatment, defined as at least 30% decrease from baseline in the average pain intensity at Week 52, based on pain intensity recordings on the tablet computer. • Pain response to treatment, defined as at least 30% decrease from Week 26 in the average pain intensity at Week 52, based on pain intensity recordings on the tablet computer. • Change from baseline to Week 12 in pain intensity scores determined using worst and current pain ratings recorded daily in the electronic diary. • Change from baseline to Week 26 in worst and current pain intensity ratings, recorded on the tablet computer. • Change from baseline to Week 52 in worst and current pain intensity ratings, recorded on the tablet computer. • Change from Week 26 to Week 52 in worst and current pain intensity ratings, recorded on the tablet computer. • Change from baseline to Week 6, Week 26, Week 36, and Week 52 in the pain intensity level of DMA. • Change from baseline to Week 6, Week 26, Week 36, and Week 52 in PPT ratios. • Change from baseline to Week 6, Week 26, Week 36, and Week 52 in the ratio of the figure of eight measurements of the affected limb versus the unaffected limb. • Change from baseline to Week 6, Week 12, Week 26, Week 36, and Week 52 in the active range of motion (AROM) ratio (affected limb and unaffected limb) measured in the hand or foot, respectively. • Change from baseline to Week 12, Week 26, and Week 52 in the CRPS Severity Score. • Patient Global Impression of Change (PGIC) at 	<p>pain intensity, based on pain intensity recordings on the tablet computer.</p> <ul style="list-style-type: none"> • Pain response to treatment, defined as at least 30% decrease from baseline in the average pain intensity, based on pain intensity recordings on the tablet computer. • Pain response to treatment, defined as at least 30% decrease from Week 26 in the average pain intensity, based on pain intensity recordings on the tablet computer. • • Change from baseline in pain intensity scores determined using worst and current pain ratings recorded daily in the electronic diary. • Change from baseline in worst and current pain intensity ratings, recorded on the tablet computer. • Change from Week 26 in worst and current pain intensity ratings, recorded on the tablet computer. • <i>Duration of effect based on average pain intensity recordings in the electronic diary.</i> • Change from baseline in the pain intensity level of DMA. • Change from baseline in PPT ratios. • Change from baseline in the ratio of the figure of eight measurements of the affected limb versus the unaffected limb. • Change from baseline in the active range of motion (AROM) ratio (affected limb and unaffected limb) measured in the hand or foot, respectively. • Change from baseline in the CRPS Severity Score. • Patient Global Impression of Change (PGIC). • Patient Global Impression of Severity (PGI-S). • Change from baseline in the EuroQoL-5 Dimension-5 level (EQ-5D-5L) index score and the health-related visual analog scale

Changes to this protocol include:	
Formerly read:	Now reads:
<p>Week 6, Week 12, Week 16, Week 22, Week 26, Week 28, Week 36, and Week 52.</p> <ul style="list-style-type: none"> • Change from baseline to Week 6, Week 12, Week 16, Week 22, Week 26, Week 28, Week 36, and Week 52 in the Patient Global Impression of Severity (PGI-S). • Change from Week 26 to Week 52 in the PGI-S. • Change from baseline to Week 12 and Week 26 in the EuroQoL-5 Dimension-5 level (EQ-5D-5L) index score and the health-related visual analog scale (VAS) score. • Change from baseline to Week 52 in the EQ-5D-5L index score and the health-related visual analog scale score. • Change from Week 26 to Week 52 in the EQ-5D-5L index score and the health-related visual analog scale score. • Change from baseline to Week 6, Week 12, Week 26, Week 28, Week 36, and Week 52 in the responses to questions on the following questionnaires (recorded on the tablet computer): <ul style="list-style-type: none"> – 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). The change from baseline to Week 16 and Week 22 will be assessed for question number 29, GLOBAL07 only. – Question EDDEP39 of the PROMIS Item Bank version 1.0 – Emotional Distress – Depression (PROMIS EDDEP39). – The 6 neuropathic pain items of the Short-Form McGill Pain Questionnaire 2 (SF-MPQ-2) (single items and the combined score). – Pain Catastrophizing Scale (PCS). – Pain Self Efficacy Questionnaire (PSEQ). 	<p>(VAS) score.</p> <ul style="list-style-type: none"> • Change from Week 26 in the EQ-5D-5L index score and the health-related VAS score. • Change from baseline in the responses to questions on the following questionnaires (recorded on the tablet computer): <ul style="list-style-type: none"> – 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). The change from baseline to Week 16 and Week 22 will be assessed for question number 29, GLOBAL07 only. – The 6 neuropathic pain items of the Short-Form McGill Pain Questionnaire 2 (SF-MPQ-2) (single items and the combined score). – Pain Catastrophizing Scale (PCS). – Pain Self Efficacy Questionnaire (PSEQ). • <i>Response to Question EDDEP39 of the PROMIS Item Bank version 1.0 – Emotional Distress – Depression (PROMIS-EDDEP39) (recorded on the tablet computer).</i> • <i>Concomitant analgesic medication use.</i>
Section 1.3.1: Inclusion criteria	
<p>6. [...] Highly effective methods of contraception must be used for at least 1 month prior to Visit 2 and for the duration of the trial.</p> <p>Male subjects must use condom and spermicide during</p>	<p>6. [...] Highly effective methods of contraception must be used for at least 1 month prior to Visit 2 and for the duration of the trial.</p>

Changes to this protocol include:	
Formerly read:	Now reads:
intercourse and must take care that the female sexual partner uses at least 1 additional method of contraception with a low failure rate defined as above, starting with Visit 2 until at least 4 weeks after the last IMP infusion.	
Section 1.3.2: Exclusion criteria	
<p>1. Evidence of renal impairment... [...]</p> <p>2. Serum calcium or magnesium outside of the central laboratory's reference range, based on central safety laboratory data obtained prior to Visit 2 (a single repeat laboratory test is allowed) [...]</p> <p>5. Subjects receiving medications with a known risk of torsades de pointes within 7 days prior to allocation. Subjects receiving selective serotonin re-uptake inhibitor antidepressants (e.g., citalopram, escitalopram) are eligible if the QT interval values do not meet the exclusion criteria, the medication was started at least 1 month prior to allocation, the dose is stable, and the dose is anticipated to remain stable throughout the trial. [...]</p> <p>17. Participation in another investigational drug trial within 3 months prior to Visit 1, or any previous trial involving neridronic acid, with the exception of subjects participating in KF7013-01 who were assigned to placebo and did not receive neridronic acid.</p>	<p>1. Evidence of <i>severe</i> renal impairment... [...]</p> <p>2. Serum calcium or magnesium outside of the central laboratory's reference range, based on central safety laboratory data obtained prior to Visit 2 (2 repeat laboratory tests <i>are</i> allowed); [...]</p> <p>5. Subjects receiving medications with a known risk of torsades de pointes within 7 days prior to allocation. Subjects receiving selective serotonin re-uptake inhibitor antidepressants (e.g., citalopram, escitalopram) are eligible if the QT interval values do not meet the exclusion criteria, the medication was started at least 1 month prior to <i>Visit 1</i>, the dose is stable, and the dose is anticipated to remain stable throughout the trial. [...]</p> <p>17. Participation in another investigational drug trial within 3 months prior to Visit 1, or any previous trial involving neridronic acid.</p>
Section 1.3.3: Criteria to continue into Treatment Period B	
<p>Up to 2 unscheduled retesting visits (with a minimum interval of 3 days) for serum calcium and/or vitamin D levels can be performed before Visit 11 if the scheduling and time window of Visit 11 is not affected. [...]</p> <p>– Evidence of renal impairment [...]</p> <p>– Serum calcium outside of the central laboratory's reference range, despite appropriate supplementation between Visit 10 and Visit 11, based on the last central safety laboratory data obtained prior to Visit 11. Two repeat laboratory tests are allowed.</p> <p>– Vitamin D deficiency prior to IMP re-allocation, defined as a 25(OH)D level less than 30 ng/mL (75 nmol/L), based on the last central safety laboratory data obtained prior to Visit 11, i.e., inability to normalize 25(OH)D levels to at least 30 ng/mL (75 nmol/L) despite appropriate supplementation between Visit 10 and Visit 11. Two repeat laboratory tests are allowed.</p>	<p><i>In case of any safety laboratory retesting, the scheduling and time window of Visit 11 must not be affected.</i> [...]</p> <p>– Evidence of <i>severe</i> renal impairment [...]</p> <p>– Serum calcium <i>or magnesium</i> outside of the central laboratory's reference range, despite appropriate supplementation between Visit 10 and Visit 11, based on the last central safety laboratory data obtained prior to Visit 11. <i>One</i> repeat laboratory test <i>is</i> allowed.</p> <p>– Vitamin D deficiency prior to IMP re-allocation, defined as a 25(OH)D level less than 30 ng/mL (75 nmol/L), based on the last central safety laboratory data obtained prior to Visit 11, i.e., inability to normalize 25(OH)D levels to at least 30 ng/mL (75 nmol/L) despite appropriate supplementation between Visit 10 and Visit 11. Two repeat laboratory tests are allowed (<i>with a minimum interval of 3 days</i>).</p>

Changes to this protocol include:	
Formerly read:	Now reads:
Section 1.4.1: Investigational medicinal products Section 10.2: Administration of investigational medicinal products	
<p>CKD-EPI Stage 3a (eGFR 45 mL/min/1.73 m² to <60 mL/min/1.73 m²) 6 mL of solution from a single vial (corresponding to neridronic acid 75 mg) will be diluted in 500 mL normal saline and administered at each treatment visit, resulting in a total dose of 300 mg neridronic acid or matching placebo.</p> <p>CKD-EPI Stage 3b (eGFR 30 mL/min/1.73 m² to <45 mL/min/1.73 m²) 5 mL of solution from a single vial (corresponding to neridronic acid 62.5 mg) will be diluted in 500 mL normal saline and administered at each treatment visit, resulting in a total dose of 250 mg neridronic acid or matching placebo.</p>	<p>CKD-EPI Stage 3a (eGFR 45 mL/min/1.73 m² to <60 mL/min/1.73 m²) 6 mL of solution from a single vial (corresponding to neridronic acid 75 mg) will be diluted in 500 mL normal saline and administered <i>by slow intravenous infusion (240 minutes [maximum 260 minutes])</i> at each treatment visit, resulting in a total dose of 300 mg neridronic acid or matching placebo.</p> <p>CKD-EPI Stage 3b (eGFR 30 mL/min/1.73 m² to <45 mL/min/1.73 m²) 5 mL of solution from a single vial (corresponding to neridronic acid 62.5 mg) will be diluted in 500 mL normal saline and administered <i>by slow intravenous infusion (240 minutes [maximum 260 minutes])</i> at each treatment visit, resulting in a total dose of 250 mg neridronic acid or matching placebo.</p>
Section 1.4.2: Prior/concomitant medications or therapies	
<p>A subject who does not take prescription analgesics is permitted to participate if considered stable and anticipated to be able to remain off prescription analgesics for the duration of the trial, up to and including Visit 8 at a minimum. Over-the-counter analgesics must also be recorded in the electronic case report form (eCRF) and remain stable throughout the trial</p> <p>[...]</p> <p>The concomitant medication must be documented in the eCRF and the sponsor must be notified.</p>	<p>A subject who does not take prescription analgesics <i>but does take over-the-counter analgesics</i> is permitted to participate if considered stable and anticipated to be able to <i>continue taking only over-the-counter and non-prescription analgesics</i> up to and including Visit 8 at a minimum. Over-the-counter analgesics must remain stable throughout the trial</p> <p>[...]</p> <p>The concomitant medication must be documented in the eCRF and the sponsor <i>or sponsor's representative (i.e., medical monitor)</i> must be notified.</p>
Section 1.4.2.1: Forbidden concomitant medications	
<p>[...]</p> <ul style="list-style-type: none"> Concomitant administration of non-steroidal anti-inflammatory drugs or any other agents with the potential to interfere with the assessment of potential changes in renal function (e.g., angiotensin converting enzyme inhibitors) until 2 weeks after the last IMP administration per treatment period, unless subjects are receiving a stable dose for at least 1 month prior to Visit 1. Non-steroidal anti-inflammatory drugs should not be used to alleviate the symptoms of the acute phase reaction and are forbidden 24 hours before and 10 hours after each IMP administration. 	<p>[...]</p> <ul style="list-style-type: none"> Concomitant administration of non-steroidal anti-inflammatory drugs or any other agents with the potential to interfere with the assessment of potential changes in renal function (e.g., angiotensin converting enzyme inhibitors) until 2 weeks after the last IMP administration per treatment period, unless subjects are receiving a stable dose for at least 1 month prior to Visit 1. Non-steroidal anti-inflammatory drugs should not be used to alleviate the symptoms of the acute phase reaction.
Section 1.5.3.1: Primary endpoint Section 14.1.7.1.1: Primary analysis	
The primary analysis will fit an MMRM to the change	The primary analysis will fit an MMRM to the change

Changes to this protocol include:	
Formerly read:	Now reads:
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 subject as random effect. An unstructured covariance matrix will be used to model the covariance structure.	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 <i>an unstructured covariance matrix to model the covariance structure of the repeated measurements.</i>
Section 1.5.3.2: Secondary efficacy endpoints Section 14.1.7.2: Analysis of the secondary efficacy endpoints	
Pain response to treatment [...] A logistic regression model will be fitted to the data, including the covariate baseline pain intensity score, and the factors geographic region, week, treatment, and treatment by week interaction as fixed effects. Model-based parameter estimates, standard errors, 95% confidence intervals, and p-values for the odds ratio at Week 12 and Week 26 between 400 mg neridronic acid and placebo will be tabulated.	Pain response to treatment [...] A logistic regression model at <i>Week 12 and Week 26</i> will be fitted to the data, including the covariate baseline pain intensity score, and the factors geographic region <i>and treatment</i> as fixed effects. Model-based parameter estimates, standard errors, 95% confidence intervals, and p-values for the odds ratio at Week 12 and Week 26 between 400 mg neridronic acid and placebo will be tabulated.
Section 1.7.1: Visit 1 to Visit 10	
Dispense/ collect electronic diary ^q ["X" at Visit 8 deleted] Training and compliance assessment for electronic diary [...] aa) Edema will only be measured in subjects reporting asymmetric edema as part of the assessment of the signs and symptoms of CRPS at baseline. The AROM will only be measured in subjects reporting decreased AROM as part of the assessment of the signs and symptoms of CRPS at baseline. b) Infusion visits should be separated by 3-day intervals to the extent possible (i.e., Day 1, Day 4, Day 7, and Day 10). Infusion visits on consecutive days are not allowed. The full dosing period should not exceed 21 days [...] c) Visit 8 must not occur prior to Day 85 in order for the subjects to have complete electronic diary data through Week 12 for the calculation of the primary endpoint. [...] m) For women of child-bearing potential, a negative dipstick urine pregnancy test result must be obtained prior to each infusion. [...] q) The electronic diary is to be returned at Visit 8 or at	Dispense electronic diary ^q Training and compliance assessment for electronic diary ["X" added at Week 16 and Week 22] [Footnote "bb" added at Visit 1 and footnote "cc" added at Visit 8] [...] aa) Edema will only be measured in subjects reporting asymmetric edema as part of the assessment of the signs and symptoms of CRPS at baseline (<i>Visit 2</i>). The AROM will only be measured in subjects reporting decreased AROM as part of the assessment of the signs and symptoms of CRPS at baseline (<i>Visit 2</i>). b) Infusion visits should be separated by 3-day intervals to the extent possible (i.e., Day 1, Day 4, Day 7, and Day 10). Infusion visits on consecutive days are not allowed. The full dosing period <i>must</i> not exceed 21 days [...] <i>bb) Compliance assessment for electronic diary not required at Visit 1.</i> c) Visit 8 must not occur prior to Day 85 in order for the subjects to have complete electronic diary data through Week 12 for the calculation of the primary endpoint. <i>cc) Training on electronic diary as, from Week 12, the electronic diary will ask for weekly assessments of pain intensity.</i> [...]

Changes to this protocol include:	
Formerly read:	Now reads:
the Early Termination Visit...	m) For women of child-bearing potential, a negative dipstick urine pregnancy test result must be obtained prior to each infusion. <i>Additional pregnancy tests to those specified may be performed if required by local law or regulations.</i> [...] q) The electronic diary is to be returned at Visit 17 or at the Early Termination Visit...
Section 1.7.2: Visit 11 to Visit 17	
Row added for “Training and compliance assessment for electronic diary” at Visit 11 to Visit 17 Row added to “Collect electronic diary” at Visit 17	
b) [...]The full dosing period should not exceed 21 days [...] i) For women of child-bearing potential, a negative dipstick urine pregnancy test result must be obtained prior to each infusion. [...] q) ... Subjects who do not meet the criteria due to a pain intensity value of less than 4 will not enter Treatment Period B, but will continue with the Follow-up Period 2. [...] t) Edema will only be measured in subjects reporting asymmetric edema as part of the assessment of the signs and symptoms of CRPS at baseline. The AROM will only be measured in subjects reporting decreased AROM as part of the assessment of the signs and symptoms of CRPS at baseline. u) The blood sample for omics testing will be collected in consenting subjects.	b) [...]The full dosing period <i>must</i> not exceed 21 days [...] i) For women of child-bearing potential, a negative dipstick urine pregnancy test result must be obtained prior to each infusion. <i>Additional pregnancy tests to those specified may be performed if required by local law or regulations.</i> [...] q) ... Subjects who do not meet the criteria <i>to continue into</i> Treatment Period B will continue with the Follow-up Period 2. [...] t) Edema will only be measured in subjects reporting asymmetric edema as part of the assessment of the signs and symptoms of CRPS at baseline (<i>Visit 2</i>). The AROM will only be measured in subjects reporting decreased AROM as part of the assessment of the signs and symptoms of CRPS at baseline (<i>Visit 2</i>). u) The blood sample for omics testing will be collected in consenting subjects. v) <i>No training needed at Visit 17.</i>
Section 3.1: Abbreviations	
eGFR Estimated glomerular filtration rate	eGFR Estimated glomerular filtration rate <i>EMA European Medicines Agency</i>
Section 8.2: Benefit/risk analysis	
The trial population described in this protocol will consist of subjects with a diagnosis of CRPS, with onset of symptoms within the last 2 years, and who are medically stable and in stable follow-up therapy for CRPS for at least 1 month. Subjects will continue to receive stable therapy for CRPS. Additional pain medication may be prescribed in the event of severe pain flare, with notification of the sponsor.	The trial population described in this protocol will consist of subjects with a diagnosis of CRPS, with onset of symptoms within the last 2 years, and who are medically stable and in stable follow-up therapy for CRPS for at least 1 month <i>prior to allocation</i> . Subjects will continue to receive stable therapy for CRPS. Additional pain medication may be prescribed in the event of severe pain flare, with notification of the sponsor <i>or sponsor’s representative (i.e., medical monitor)</i> .

Changes to this protocol include:	
Formerly read:	Now reads:
<p>[...] <i>Acute phase reaction</i> The most common side effects associated with parenteral administration of aminobisphosphonates are flu-like symptoms, commonly referred to as “acute phase reaction” (Reid et al. 2010; Silverman et al. 2011). Symptoms include fever, myalgia, fatigue, headache, diarrhea, arthralgia, muscle pain, and bone pain.</p> <p>[...] As there are currently no Food and Drug Administration (FDA) approved treatments for CRPS...</p>	<p>[...] <i>Acute phase reaction</i> The most common side effects associated with parenteral administration of aminobisphosphonates are flu-like symptoms, commonly referred to as “acute phase reaction” (Reid et al. 2010; Silverman et al. 2011). Symptoms include fever, myalgia, fatigue, headache, diarrhea, arthralgia, and bone pain.</p> <p>[...] As there are currently no FDA or EMA approvals for <i>specific pharmacological</i> treatments for CRPS...</p>
Section 9.3.2: Subject discontinuation from the IMP	
<p>Table 2: Reasons for permanent and temporary discontinuation of subjects from IMP</p> <p>[...] Evidence suggestive of a possible change in renal function:</p> <p>[...]</p> <ul style="list-style-type: none"> • A persistent increase of urinary ACR based on values >300 mg/g (quantitative urinary albumin and creatinine data from the central laboratory); and ≥150 mg/g (quantitative urinary albumin and creatinine data from the central laboratory) from urine samples obtained at least 1 week apart. <p>[...]</p> <ul style="list-style-type: none"> • A persistent eGFR <30 mL/min/1.73 m² based on repeated quantitative data from the central laboratory, with blood and urine samples obtained at least 1 week apart. <p>[...]</p> <p>a) Not applicable if no eGFR value after first IMP administration is available.</p>	<p>Table 2: Reasons for permanent and temporary discontinuation of subjects from IMP</p> <p>[...] <i>Test results</i> suggestive of a possible change in renal function:</p> <p>[...]</p> <ul style="list-style-type: none"> • A persistent urinary ACR based on <i>an initial value</i> >300 mg/g (<i>semi-quantitative dipstick or</i> quantitative urinary albumin and creatinine data from the central laboratory) and <i>on a second value</i> ≥150 mg/g (quantitative urinary albumin and creatinine data from the central laboratory) from urine samples obtained at least 1 week apart. <p>[...]</p> <ul style="list-style-type: none"> • A persistent eGFR <30 mL/min/1.73 m² based on repeated quantitative data from the central laboratory, with urine samples obtained at least 1 week apart. <p>[...]</p> <p>a) Not applicable if no eGFR value after first IMP administration is available. <i>For both treatment periods, the last value observed prior to first IMP application in Treatment Period A will be used for calculating the decrease in eGFR.</i></p>
Section 11.1.1.1: Visit 1 (Day -60 to Day -8)	
<ul style="list-style-type: none"> • Training and compliance assessment for electronic diary. 	<ul style="list-style-type: none"> • Training for electronic diary.
Section 11.1.2: Treatment Period A Section 11.1.4.2: Treatment Period B	
<p>[...] The full dosing period should not exceed 21 days from the first infusion...</p>	<p>[...] The full dosing period <i>must</i> not exceed 21 days from the first infusion...</p>
Section 11.1.3.3: Visit 8 (Day 85 [Week 12]; +7 days)	
<ul style="list-style-type: none"> • Collect electronic diary. 	<ul style="list-style-type: none"> • <i>Training on</i> electronic diary <i>as, from Week 12, the</i>

Changes to this protocol include:	
Formerly read:	Now reads:
	<i>electronic diary will ask for weekly assessments of pain intensity.</i>
Section 11.1.3.4: Visit 9 (Day 113 [Week 16]; ±4 days) Section 11.1.3.5: Visit 10 (Day 155 [Week 22]; ±4 days) Section 11.1.4.1: Visit 11 (Day 183 [Week 26]; +7 days) Section 11.1.4.2.1: Visit 12 (Day 186; ±1 day) - only subjects receiving a second treatment course Section 11.1.4.2.2: Visit 13 (Day 189; ±1 day) - only subjects receiving a second treatment course Section 11.1.4.2.3: Visit 14 (Day 192; ±1 day) - only subjects receiving a second treatment course Section 11.1.4.3: Visit 15 (Day 197 [Week 28]; +7/-2 days) - only subjects receiving a second treatment course Section 11.1.4.4: Visit 16 (Day 253 [Week 36]; ±7 days) - for all subjects	
• Check trial discontinuation criteria...	<ul style="list-style-type: none"> • <i>Compliance assessment for electronic diary.</i> • Check trial discontinuation criteria...
Section 11.1.4.1: Visit 11 (Day 183 [Week 26]; +7 days)	
Subjects who do not meet the criteria due to a pain intensity value of less than 4 will not enter Treatment Period B, but will continue with the Follow-up Period 2.	Subjects who do not meet the criteria <i>to continue into</i> Treatment Period B will continue with the Follow-up Period 2.
Section 11.1.4.5: Visit 17 (Day 365 [Week 52]; +7 days) - for all subjects	
• Complete the assessment of the signs and symptoms of CRPS.	<ul style="list-style-type: none"> • Complete the assessment of the signs and symptoms of CRPS. • <i>Compliance assessment for electronic diary.</i> • <i>Collect electronic diary.</i>
Section 11.3.2: Meals and fluid intake restrictions	
Visits 2, 6, 7, 8, 10, 15, 16, and 17 should be attended in a fasting state (at least 8 hours). Light meals are allowed after sampling for bone turnover markers and may be provided before and/or after IMP infusions...	Visits 2, 6, 7, 8, 10, 15, 16, and 17 should be attended in a fasting state (at least 8 hours). Light meals are allowed after sampling for bone turnover markers and may be provided before, <i>during</i> , and/or after IMP infusions...
Section 12.2.2: Prior and concomitant medication or therapies	
All medication requiring prescriptions (including oral contraceptives), over-the-counter medication (including herbals and vitamins), and therapies (including medical devices and therapies such as e.g., massage or cognitive behavioral therapy) used within 3 months prior to enrollment and up to the end of the trial must be recorded in the eCRF. Any change in dosage, regimen, frequency, or route, must be recorded in the eCRF as a new entry.	All medication requiring prescriptions (including oral contraceptives), over-the-counter medication (including herbals and vitamins), and therapies (including medical devices and therapies such as e.g., massage or cognitive behavioral therapy) used within 3 months prior to enrollment and up to the end of the trial must be recorded in the eCRF. <i>All failed CRPS medication must be added in the eCRF (including medications stopped before 3 months prior to enrollment).</i> Any change in dosage, regimen, frequency, or route, must be recorded in the eCRF as a new entry.
Section 12.2.3.1: Diagnosis of CRPS	
Distal to mid-limb involvement (typically hand or foot), with or without proximal spread, should be present. [...] Diagnosis of CRPS involving an atypical body part	Distal to mid-limb involvement (typically hand or foot), with or without proximal spread, <i>must</i> be present. [...] <i>Ongoing, disproportionate pain and a lack of other</i>

Changes to this protocol include:	
Formerly read:	Now reads:
(e.g., trunk, breasts, pelvic regions, lower back, face) is not permitted for this trial.	<i>diagnosis that better explains the signs and symptoms must also be confirmed at the Enrollment Visit.</i> Diagnosis of CRPS involving an atypical body part (e.g., trunk, breasts, pelvic region, lower back, face, shoulder, or hip) is not permitted for this trial.
Section 12.2.4.2: Urine drugs of abuse test	
[...] Subjects who are receiving stable doses of prescribed medications containing amphetamines, benzodiazepines or opioids will not be excluded from the trial even if the test is positive.	[...] Subjects who are receiving stable doses of prescribed medications containing amphetamines, benzodiazepines, <i>cannabinoids</i> , or opioids will not be excluded from the trial even if the test is positive.
Section 12.3.1.1: Electronic diary	
Subjects will be 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 will be for a 24-hour recall period.	Subjects will be 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 will be for a 24-hour recall period. <i>After Visit 8 up to Visit 17, subjects will be 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.</i>
Section 12.3.2: Dynamic mechanical allodynia	
[...] A value of “10” corresponds to the individual maximum pain imaginable. The tactile stimulus is tested 5 times. The degree of pain...	[...] A value of “10” corresponds to the individual maximum pain imaginable. The tactile stimulus is tested 5 times. <i>If the subject reports a value of “10”, then no further test will be performed for the respective visit.</i> The degree of pain...
Section 12.3.5: Active range of motion measurement	
For subjects having decreased AROM at baseline (diagnosed based on clinical judgment; sign “Motor abnormalities” ticked “yes”, sub-category “decreased AROM” ticked “yes” on the CRPS Severity Score at baseline), both...	For subjects having decreased AROM at baseline (diagnosed based on clinical judgment; sign “Motor abnormalities” ticked “yes”, sub-category “decreased AROM” ticked “yes” on the CRPS Severity Score at baseline [<i>Visit 2</i>]), both...