SDR-PRO-TEMPLATE-02

Trial code:	KF7013-03
Title of trial:	Open-label safety trial of intravenous neridronic acid in subjects with complex regional pain syndrome (CRPS)
Brief title:	Safety of intravenous neridronic acid in CRPS
Indication:	Treatment of CRPS
International coordinating investigator: [a]	[redacted] MD Universitätsmedizin der Johannes Gutenberg-Universität Mainz Klinik und Poliklinik für Neurologie Langenbeckstrasse 1, 55131 Mainz, Germany Telephone: +49 (0) 613-117-[redacted]
Trial sites:	Multi-site trial (approximately 70 sites in the United States and European Union) Documentation of the involved trial sites will be maintained.
Trial sponsor:	Grünenthal GmbH, 52099 Aachen, Germany
Sponsor's medically qualified person / Sponsor's signatory: [a]	[redacted] MD, International Clinical Lead
Public contact point:	Email: clinical-trials@grunenthal.com; Telephone: +49 (0) 241-569-3223

a) Contact detail changes during the course of the trial will be documented and do not require a protocol amendment.

Version	**Date**	**DMS version number**	**Valid for**
Original:	19 Jul 2016	1.0	All countries
Amendment 01:	21 Oct 2016	2.0	All countries
Amendment 02	20 Mar 2017	3.0	Germany
Amendment 03	19 Apr 2017	4.0	All countries
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IND number:	115811 (US sites only)	**EudraCT number:**	2016-001164-11
Universal Trial Number:	U1111-1180-8099		

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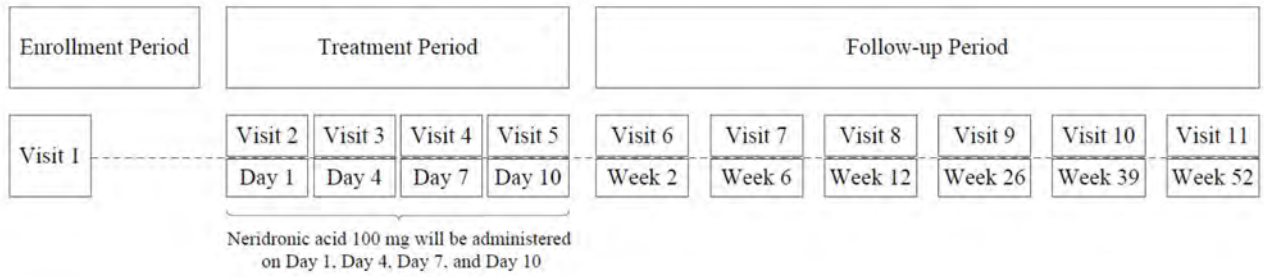
1 PROTOCOL SYNOPSIS

1.1 Trial design

This is a multi-site, open-label, single-arm, Phase III safety trial of intravenous neridronic acid in subjects with CRPS.

1.1.1 Flow diagram summary of the trial



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, a treatment period consisting of 4 infusions over 10 days, and a follow-up period of approximately 50 weeks (Visit 6 [Week 2] through Visit 11 [Week 52]). The subjects are expected to be in the trial for approximately 60 weeks (14 months). See Section 1.1.1 for a summary of the trial as a flow diagram and Section 1.6 for a tabular schedule of events.

1.2 Trial objectives, endpoints, and outcomes

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

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

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

- Occurrence of permanent discontinuation from treatment due to deterioration in renal function.

To assess the bone safety of neridronic acid in subjects with CRPS

- Occurrence of signs of osteomalacia, based on histology and quantitative bone histomorphometry, in subjects undergoing bone biopsy.

To assess the efficacy of neridronic acid in treatment of CRPS

- Change from baseline to Week 12 and Week 26 in the worst pain intensity score, using a NRS.
- Change from baseline to Week 12 and Week 26 in the average pain intensity score, using a NRS.
- Change from baseline to Week 12 and Week 26 in the Pain Disability Index (PDI) score.
- 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 12 and Week 26 in the Pain Anxiety Symptom Scale (PASS) score.
- Change from baseline to Week 12 and Week 26 in the Center for Epidemiological Studies Depression Scale (CES-D) score.
- Change from baseline to Week 12 and Week 26 in the CRPS Severity Score.

To assess the pharmacodynamics of neridronic acid in subjects with CRPS

- Change from baseline to Week 12 and Week 26 in concentrations of bone turnover markers (C-terminal telopeptide of type I collagen [CTX], bone alkaline phosphatase [BAP], and procollagen type I amino-terminal propeptide [PINP]) in serum.
- Change from baseline to Week 26 in bone mineral density (BMD) in the lumbar spine in subjects undergoing dual-energy X-ray absorptiometry (DXA; US sites only).
- Change from baseline to Week 26 in BMD in regions of interest (ROIs) of the CRPS-affected limb, relative to the contralateral limb, in subjects undergoing DXA (US sites only).
- Change from baseline to Week 26 in volume of bone marrow lesions in ROIs of the CRPS-affected limb, relative to the contralateral limb, in subjects undergoing magnetic resonance imaging (MRI; US sites only).

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

- Work Productivity and Activity Impairment Questionnaire: CRPS (WPAI: CRPS) assessment on Day 1, at Week 26, and at Week 52.
- Medical resources utilization and health economics data collection on Day 1, at Week 26, and at Week 52.

1.3 Trial subjects – the population to be studied

1.3.1 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.
4. Ongoing moderate to severe chronic pain, including a baseline current pain intensity score of ≥4 using an 11-point NRS, referring to the CRPS-affected limb, at Visit 2 (prior to dosing).
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 trials of at least 2 treatments for CRPS, one of which must be a pharmacologic treatment (see Section 1.4.3).
6. Women of child-bearing potential must have a negative urine beta-human chorionic gonadotropin (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 <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 impairment).

1.3.2 Exclusion criteria

1. Evidence of renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine equation [Levey et al. 2009] or a urinary albumin creatinine ratio [ACR] >150 mg/g), based on central safety laboratory data obtained prior to Visit 2, or a history of chronic kidney disease. Note: a single repeat laboratory test is allowed.
2. Serum calcium or magnesium values 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); a history of hypocalcemia or a metabolic disorder anticipated to increase risk for hypocalcemia (e.g., hypoparathyroidism); concomitant use of drug(s) with known potential to cause hypocalcemia (e.g., aminoglycosides).
3. Vitamin D deficiency, defined as a 25(OH)D level <30 ng/mL, 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 must be documented prior to allocation to investigational medicinal product (IMP).

4. Corrected QT interval (according to Fridericia's formula; QTcF) >470 ms (average of 3 electrocardiograms [ECGs] obtained at Visit 1); serum potassium outside the central laboratory's reference range at Visit 1; 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 other known risk factor for torsade de pointes.
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, escotalopram) or tricyclic antidepressants 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 until at least 4 days after the last infusion of IMP.
6. Anticipated requirement for treatment with oral or intravenous bisphosphonate for another condition such as osteoporosis during the trial, or administration of denosumab (Prolia®) or other drugs affecting bone turnover or bone metabolism 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 predispose 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 2.
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 >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, ≥3 days apart, are ≤2-fold upper limit of normal.

17. Participation in another investigational drug trial within 3 months prior to Visit 1 or any previous trial with neridronic acid, with the exception of subjects participating in KF7013-01 who were assigned to placebo and did not receive 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 1.4.3).
20. Subjects incapable of signing the informed consent.

1.4 Trial treatments

1.4.1 Investigational medicinal products

The first batch of IMP will be provided to sites in the US in glass ampules, each containing 108 mg sodium neridronate hemi hydrate (equivalent to 100 mg neridronic acid) in a total volume of 8 mL. Subsequent batches of IMP will be supplied in vials.

Sites in the EU will receive all batches of IMP in glass vials.

The full contents of a single ampule or 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.

1.4.2 Other medication

Tetracycline hydrochloride 250 mg capsules for oral administration (applicable only for the subset of subjects at US sites undergoing the bone biopsy).

1.4.3 Prior/concomitant medications or therapies

Enrolled subjects must have failed trials of at least 2 treatments for CRPS, 1 of which must be a pharmacologic treatment. A failed trial is defined by continuing pain. Such treatments may be prior to or continuing at enrollment and can include any analgesic medication (including non-steroidal anti-inflammatory drugs [NSAIDs], opioids, antidepressants, etc.), interventional therapy (e.g., nerve block or spinal cord stimulation), or physical therapy.

Subjects are encouraged to continue standard of care interdisciplinary treatment for CRPS, including follow-up for physical therapy, occupational therapy, cognitive behavioral therapy, and graded motor imagery (including mirror feedback).

Subjects may continue treatment with allowed concomitant medications and therapies, including opioids and other analgesics, if they are on a stable, well-defined treatment regimen for at least 1 month prior to treatment and are anticipated to be able to maintain the treatment regimen, in the opinion of the investigator. Stable 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. Changes to concomitant medications and therapies (e.g., use of short acting opioids for CRPS flares) may be allowed during the course of the trial and must be discussed with the medical monitor and documented in the case report form (CRF).

Sites will provide subjects with supplemental calcium and vitamin D, starting from Visit 1 and continuing through to the end of the trial. Acetaminophen (paracetamol) is recommended for

prophylaxis and treatment of flu-like symptoms that are commonly associated with the first intravenous administration of bisphosphonates (see Section 8.2 for details).

The following are forbidden as concomitant medications and therapies during the trial:

- Drugs with the potential to cause hypocalcemia (e.g., aminoglycosides). Subjects on a stable dose of furosemide or other loop diuretics may receive treatment with IMP as long as no dosage changes in the diuretic medications are anticipated and calcium levels are in the reference ranges.
- Oral or intravenous bisphosphonates, calcitonin, denosumab, or other bone-active drugs (e.g., teriparatide).
- High-dose opioid analgesics (>200 mg morphine equivalent daily dose) or combinations of opioids and benzodiazepines or any other treatment regimen 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).
- Nerve blocks, radiofrequency ablation or other sympathectomy procedures, hyperbaric oxygen treatments, ketamine infusions, intravenous immunoglobulin, or other experimental therapies.
- Investigational drugs.

The following medications and therapies are forbidden from 7 days prior to allocation until 4 days after the last infusion:

- Drugs with a known risk of torsades de pointes, excluding selective serotonin re-uptake inhibitor antidepressants (e.g., citalopram, escitalopram) and tricyclic antidepressants if QT interval values met entry criteria, subjects were on a stable dose for at least 1 month prior to allocation, and doses are expected to stay stable throughout the trial.

1.5 Statistical analyses

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

1.5.1 Sample size rationale

The sample size is intended to maximize available safety data in line with the FDA regulatory requirements to support product registration. It is estimated that approximately 290 subjects will be included in this trial.

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

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

1.5.3 Statistical methods and analysis

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

Primary safety endpoint

The primary endpoint of this trial is a binary endpoint assessing whether or not a subject experienced any TEAE. The primary safety endpoint will be analyzed in the SAF.

Secondary safety endpoints and other safety data

The incidences and incidence rates of all adverse events will be summarized descriptively.

Permanent discontinuations from treatment due to adverse events will be summarized descriptively.

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

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

All safety analyses will be conducted on the Safety Set.

Secondary efficacy endpoints and other efficacy data

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

All efficacy analyses will be conducted on the Full Analysis Set.

Handling of missing data

Missing data will not be imputed in this trial. The number of missing data will be included in all descriptive summaries.

A mixed-effects model for repeated measurements (MMRM) will be conducted on the observed values of the change in current pain intensity score. An MMRM leads to unbiased estimates if the missingness mechanism is missing-at-random. Due to the long-acting effect of neridronic acid, missing-at-random is considered a clinically plausible assumption. The MMRM in this trial will include pooled site, baseline pain intensity and week as fixed effects and subject as a random effect. An unstructured covariance matrix will be used to model the covariance structure. Least squares means, standard errors, and 95% confidence intervals for the change from baseline will be obtained.

1.6 Schedule of events

	Enrollment Period	Treatment Period				Follow-up Period					
	Visit 1 [a]	Visit 2	Visit 3 [b]	Visit 4 [b]	Visit 5 [b]	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Trial procedure	Day -60 to Day -1	Day 1	Day 4 (±1 day)	Day 7 (±1 day)	Day 10 (±1 day)	Week 2 (±2 days)	Week 6 (±7 days)	Week 12 (±7 days)	Week 26 (±15 days)	Week 39 (±15 days)	Week 52 (±15 days)
Obtain written informed consent	X										
Record demographic data	X										
Record medical history [d]	X										
Record dental history [e]	X										
Dispense calcium and vitamin D supplements [f]	X										
Record prior medications and therapies	X										
Review inclusion/exclusion criteria [g]	X	X									
Check subject discontinuation criteria		X	X	X	X	X	X	X	X	X	
Check IMP suspension criteria [i]		X	X	X	X						
Record physical examination outcome [k]	X	X						X	X	X	X
Record vital signs [l]	X	X	X	X	X	X	X	X	X	X	X
Record 12-lead ECG [m]	X	X	X	X	X	X			X		X

	Enrollment Period	Treatment Period				Follow-up Period					
	Visit 1 [a]	Visit 2	Visit 3 [b]	Visit 4 [b]	Visit 5 [b]	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Trial procedure	Day -60 to Day -1	Day 1	Day 4 (±1 day)	Day 7 (±1 day)	Day 10 (±1 day)	Week 2 (±2 days)	Week 6 (±7 days)	Week 12 (±7 days)	Week 26 (±15 days)	Week 39 (±15 days)	Week 52 (±15 days)
Perform continuous real-time ECG monitoring		X	X	X	X						
Record concomitant medications and therapies	X	X	X	X	X	X	X	X	X	X	X
Ask the subject to complete pain intensity assessments	X	X	X	X	X	X	X	X	X	X	X
Ask the subject to complete the PGIC							X	X	X	X	X
Ask the subject to complete the BPI interference scale		X					X	X	X	X	X
Ask the subject to complete the PDI		X					X	X	X	X	X
Ask the subject to complete the EQ-5D-5L		X					X	X	X	X	X
Ask the subject to complete the PASS		X					X	X	X	X	X
Ask the subject to complete the CES-D		X					X	X	X	X	X
Ask the subject to complete the WPAI: CRPS [w]		X							X		X
Collect medical resources utilization and health economics data [w]		X							X		X

	Enrollment Period	Treatment Period				Follow-up Period					
	Visit 1 [a]	Visit 2	Visit 3 [b]	Visit 4 [b]	Visit 5 [b]	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Trial procedure	Day -60 to Day -1	Day 1	Day 4 (±1 day)	Day 7 (±1 day)	Day 10 (±1 day)	Week 2 (±2 days)	Week 6 (±7 days)	Week 12 (±7 days)	Week 26 (±15 days)	Week 39 (±15 days)	Week 52 (±15 days)
Complete the assessment of the signs and symptoms of CRPS [o]	X	X					X	X	X	X	X
Take blood for safety laboratory	X	X	X	X	X	X	X	X	X	X	X
Collect urine for urinalysis [p]	X	X	X	X	X	X	X	X	X	X	X
Take blood (in the morning) for bone turnover marker evaluation [r]		X				X	X	X	X	X	X
Perform a urine ß-HCG pregnancy test [s]	X	X	X	X	X				X		X
Perform urine drugs of abuse testing	X										
Provide subject trial card	X										
Collect subject trial card [t]									X		X
Perform bone imaging [u, w]	X								X		
Perform bone biopsy [v, w]									X		
Prescribe tetracycline [x]								X			
Tetracycline dosing diary for recording tetracycline intake [x]								dispense	collect		
Record adverse events [n]	X	X	X	X	X	X	X	X	X	X	X

	Enrollment Period	Treatment Period				Follow-up Period					
	Visit 1 [a]	Visit 2	Visit 3 [b]	Visit 4 [b]	Visit 5 [b]	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Trial procedure	Day -60 to Day -1	Day 1	Day 4 (±1 day)	Day 7 (±1 day)	Day 10 (±1 day)	Week 2 (±2 days)	Week 6 (±7 days)	Week 12 (±7 days)	Week 26 (±15 days)	Week 39 (±15 days)	Week 52 (±15 days)
Allocate to IMP [h]		X									
Administer IMP [j]		X	X	X	X						

All visits, except Visit 1, should be attended in a fasting state (at least 8 hours).

a) Baseline imaging assessments must be scheduled during the enrollment period for subjects undergoing DXA and MRI. Additional visits are allowed during the enrollment period to confirm normalization of safety laboratory values (e.g., for subjects with vitamin D deficiency). 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.

b) The target dosing schedule is Day 1, Day 4, Day 7, and Day 10. Flexibility of ±1 day is allowed for Day 4, Day 7, and Day 10, keeping the overall duration of the infusions within the 10-day period (11 days if Day 10 +1 day). A minimum period of 48 hours is required between infusions. In situations where treatment is temporarily discontinued (e.g., due to a potential safety concern or scheduling issue), and a decision is made (in consultation with the sponsor or sponsor's designee) to resume treatment, the treatment period can be extended up to 21 days (i.e., Visit 5 should occur no later than 21 days after Visit 2).

d) Includes history of CRPS (date, location and type of precipitating event; date of onset of symptoms; date of diagnosis; specific location of signs and symptoms; and specific body site where diagnostic criteria are applied).

e) Dental history will include: date of last dental visit; dental extractions and other invasive dental surgery in 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 predispose to risk of medication-related osteonecrosis of the jaw.

f) 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.

g) Compliance with inclusion and exclusion criteria must be confirmed before allocation to IMP, including pain score of at least 4 on the NRS.

h) Allocation must be performed using the interactive response technology system.

i) Subjects must be assessed prior to each infusion. This includes assessment for signs and symptoms of ocular inflammation, signs of proteinuria (see footnote p), and signs of dehydration. Subjects must be well hydrated prior to the start of infusions. Central safety laboratory data from the previous visit, in particular eGFR, must be evaluated prior to each infusion.

j) All baseline measurements (including blood sampling for hematology and clinical chemistry, urinalysis, ECG, vital signs, and physical examination) must be completed and results available 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]).

k) After Visit 1, record any changes from the previous visit.

l) At Visit 2 through Visit 5, vital signs will be taken once at least 15 minutes before the infusion and once at least 15 minutes after the infusion. Body weight will be included as a vital sign and will be measured at all visits (only once at Visit 2 to Visit 5, prior to the infusion).

m) At Visit 2 through Visit 5, triplicate ECGs will be recorded once at least 15 minutes before the infusion and once at least 15 minutes after the infusion. A triplicate ECG will be recorded for all other visits.

n) Subjects should be queried for any events occurring since the previous visit; any events noted at Visit 1 should be documented as medical history or as part of physical examination results.

o) The diagnosis of CRPS must be confirmed using the tablet computer at Visit 1 according to the clinical diagnostic criteria recommended by the IASP (Budapest clinical criteria) (Section 12.2.3.1). The number of signs and symptoms of CRPS at Visit 2, and Visit 7 to Visit 11, inclusive, will be summed for determination of the CRPS Severity Score (Section 12.4.8).

p) At Visit 2 through Visit 5, urine collection must be performed prior to infusion. In addition to the sample for central safety laboratory analysis, a local dipstick evaluation for determination of urinary albumin creatinine ratio must be performed prior to the start of infusion.

r) C-terminal telopeptide of type I collagen (CTX), bone alkaline phosphatase (BAP), and PINP (procollagen type I amino-terminal propeptide).

s) For women of child-bearing potential, a negative urine pregnancy test result must be obtained prior to each infusion. For subjects who discontinue the trial prior to completion, pregnancy testing should be performed at the Early Termination Visit (whose procedures are identical to Visit 11).

t) The subject card is to be returned at the final visit or at the Early Termination Visit in the case of early discontinuation from the trial.

u) It is planned to perform bone densitometry (DXA) and MRI in a subset of 30 subjects.

v) A single bone biopsy will be obtained from the iliac crest, following tetracycline double-labeling, in a subset of subjects. The biopsy should be scheduled to be performed 26 weeks after the first administration of IMP. It is planned to obtain approximately 15 evaluable bone biopsy samples from approximately 20 subjects.

w) At US sites only.

x) For US subjects undergoing bone biopsy only.

ß-HCG = beta-human chorionic gonadotropin, BPI = Brief Pain Inventory, CES-D = Center for Epidemiological Studies Depression Scale, CRPS = complex regional pain syndrome, DXA = dual-energy X-ray absorptiometry, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, EQ-5D-5L = EuroQol-5 dimension 5 level, IASP = International Association for the Study of Pain, IMP = investigational medicinal product, MRI = magnetic resonance imaging, NRS = numerical rating scale, PASS = Pain Anxiety Symptom Scale, PDI = Pain Disability Index, PGIC = Patient Global Impression of Change, WPAI = Work Productivity and Activity Impairment Questionnaire.

1.7 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.

2 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

3.1 Abbreviations

Abbreviation	Explanation
ACR	Albumin creatinine ratio
β-HCG	Beta-human chorionic gonadotropin
BAP	Bone alkaline phosphatase
BMD	Bone mineral density
BPI	Brief Pain Inventory
CES-D	Center for Epidemiological Studies Depression Scale
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case report form
CRO	Contract research organization
CRPS(-I)(-II)	Complex regional pain syndrome (Type I) (Type II)
CTX	C-terminal telopeptide of type I collagen
DMC	Data monitoring committee
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
EFPIA	European Federation of Pharmaceutical Industries and Associations
eGFR	Estimated glomerular filtration rate
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
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IMP	Investigational medicinal product
IRB	Institutional review board
IRT	Interactive response technology
MDMA	3,4-methylendioxy methamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model for repeated measurements
MRI	Magnetic resonance imaging
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drug
ONJ	Osteonecrosis of the jaw
PASS	Pain Anxiety Symptom Scale
PDI	Pain Disability Index
PGIC	Patient Global Impression of Change

Abbreviation	Explanation
PINP	Procollagen type I amino-terminal propeptide
QTcB	QT interval (corrected according to Bazett's formula)
QTcF	QT interval (corrected according to Fridericia's formula)
ROIs	Regions of interest
SAE	Serious adverse event
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 allocated 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.
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 who 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.
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 an enrollment failure.
Treated subjects	Subjects with at least 1 administration of IMP.
Treatment completers	Treated subjects who completed IMP administration according to the protocol, i.e., subjects who received the full dose of all 4 planned infusions of IMP.

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/or 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.

Separate informed consent will be required from subjects participating in the bone biopsy assessment. Participation in the bone biopsy assessments will not be mandatory for participation in the trial.

Separate informed consent will be required from subjects participating in the imaging (DXA and MRI) assessments. Participation in these imaging evaluations is not mandatory for trial participation.

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 the time of 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.

Country-specific coordinating investigators will be defined who are responsible for the coordination of principal investigators at multiple trial sites in 1 country.

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 (CROs; commercial, academic or other, e.g., central laboratory facilities, trial supply management provider, electronic patient reported outcome 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.

5.4 Data monitoring committee

An external, independent data monitoring committee (DMC) will periodically review safety information from the trial and monitor trial conduct and overall progress.

The DMC will have the ability to make recommendations to the sponsor that might impact the future conduct of the trial. Procedures for and management of the DMC will follow the sponsor's standard operating procedures (SOPs) and will be documented in the DMC Charter. The DMC for this trial is anticipated to convene approximately every 6 months, depending on subject accrual in the trial.

6 INTRODUCTION AND TRIAL BACKGROUND

6.1 Introduction

Complex regional pain syndrome is a chronic, severe and frequently 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). CRPS 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 approved pharmacological treatments for CRPS in the US, 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 indicate 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 open-label trial with a total dose of neridronic acid 400 mg is designed to obtain 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.

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.

More than 500 subjects have received parenteral neridronic acid in Phase II and Phase III trials intended for registration of intravenous or intramuscular formulations for the treatment of osteogenesis imperfecta, Paget's disease, osteoporosis, and CRPS-I. Doses administered in these trials ranged from 12.5 mg to 400 mg, with the 400 mg dose administered as either a single intravenous infusion of approximately 5 hours, or divided into four 2-hour infusions of 100 mg administered over 10 days. Based on results of these trials, neridronic acid appears safe and well tolerated up to a dose of 400 mg as a single or divided infusion. Drug-related adverse events following intravenous and intramuscular administration of neridronic acid consisted predominantly

of fever and flu-like symptoms (e.g., arthralgia, myalgia) following the first administration, as well as pain, bruising, and tenderness at the injection site for intramuscular injections. Mean decreases in calcium and phosphate were noted in serum chemistry assessments, although individual subject out-of-range values and symptomatic hypocalcemia were rare. Based on these findings, the adverse event profile of neridronic acid is considered to be similar to that of other aminobisphosphonates. The safety of neridronic acid is supported by spontaneous adverse event reporting, pharmacovigilance, and information from published trials.

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, active range of motion, hyperalgesia, and allodynia, also showed significant improvements (Varenna 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. These results suggest intravenous neridronic acid 400 mg is effective and safe for treatment of CRPS-I.

6.4 Trial rationale

The aim of this trial is to investigate the safety of intravenous neridronic acid in patients with CRPS. The trial is intended as an integral part of the overall safety assessment of neridronic acid, to support submission to regulatory agencies for product registration.

7 TRIAL OBJECTIVES AND ENDPOINTS

The trial objectives and endpoints are given in Section 1.2.

8 TRIAL DESIGN

8.1 Discussion of the trial design

This is a multi-site, open-label, single-arm, Phase III trial. A single-arm trial, without a placebo or other comparator, maximizes the number of subjects exposed to neridronic acid and is intended to provide adequate safety data to support product registration. Although efficacy assessments are included for exploratory purposes, results of these evaluations must be interpreted with caution in the absence of a comparator arm.

A subset of subjects will undergo iliac crest bone biopsy to assess bone histology and histomorphometry indices following treatment with neridronic acid 400 mg. The effect of neridronic acid on bone quality and mineralization was evaluated in biopsies from 14 patients with Paget's disease receiving neridronic acid 250 mg (50 mg/day for 5 days; McCloskey et al. 1987; Atkins et al. 1987). Normal bone mineralization and bone formation were observed in biopsies from regions of non-pagetic bone (iliac crest), and improved indices of bone turnover were observed in

regions of pagetic bone. It is planned to obtain approximately 15 evaluable bone biopsy specimens from approximately 20 subjects. It is anticipated that bone biopsy specimen evaluation will confirm normal bone mineralization in the iliac crest at approximately 6 months following treatment with neridronic acid 400 mg. A 6 month time point was selected for the biopsy in order to match the slow kinetics of bone matrix and mineral apposition in humans, with approximately 6 months required to complete a single remodeling cycle (Riggs and Parfitt 2005).

It is anticipated that a subset of 30 subjects will undergo bone densitometry and MRI to assess the effect of neridronic acid on BMD and bone marrow lesions in CRPS-affected limbs, relative to the contralateral, unaffected limb. The same subject will be allowed to participate in both bone biopsy and bone densitometry and MRI sub studies if they are willing. This exploratory investigation is anticipated to corroborate published descriptions of decreased BMD and other bone abnormalities in the affected limbs of subjects with CRPS (Gatti et al. 2016) and may provide a foundation for future investigation of the effect neridronic acid on bone pathology in CRPS.

Rationale for the trial population

The trial population will include subjects with both CRPS-I and CRPS Type II (CRPS-II). Subjects with CRPS-II are poorly represented in clinical trials. However, the distinctions between these two subtypes are not always clear (Oaklander and Horowitz 2015; Bruehl 2015). Inclusion of subjects with CRPS-II is not anticipated to affect the safety objectives of this trial.

8.1.1 Rationale for the investigational medicinal product and the selected dose

A placebo-controlled trial in 82 subjects with CRPS-I indicated that 400 mg of neridronic acid, administered as four 2-hour infusions of 100 mg in 10 days, is safe, well-tolerated and effective for treatment of pain and other symptoms of CRPS (Varenna et al. 2013).

A pilot trial of neridronic acid involving cumulative intravenous doses of 200 mg, 300 mg, and 400 mg neridronic acid in patients with CRPS-I suggested that the 400 mg cumulative dose was optimally effective. As the 4 x 100 mg dose regimen 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 neridronic acid 100 mg to treat Paget's disease of bone, osteogenesis imperfecta, and CRPS-I is 2 hours. To limit the maximum concentrations (C_{max}) in this trial to levels similar to those obtained in the KF7013-01 trial, in which neridronic acid 62.5 mg was infused in 2 hours, the infusion time has been extended to 4 hours.

Alternative dosage forms or routes of administration for neridronic acid are limited to an intramuscular dosage form (25 mg per ampule, available in Italy), which would be impractical for administering a 400 mg total dose. An oral dosage form is not available and would have practical limitations due to the very low bioavailability of bisphosphonates (typically reported in the range of 1%).

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

The number of visits and visit frequency are the same as those in the previous KF7013-01 trial and are considered sufficient to assure subject safety and meet study objectives.

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 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. Changes in analgesic medications and other treatments for CRPS may be permitted during the follow-up period. This will help to ensure that subjects in the trial will not suffer from untreated pain. 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, muscle pain, 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, starting from approximately 1 hour prior to the first infusion and then approximately every 6 hours for the 72-hour period after the first infusion. Commercially available products and dosages 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 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.

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 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. Recommended doses are 500 mg to 1000 mg per day elemental calcium and approximately 1000 IU/day vitamin D. A combination product of calcium and vitamin D may be used. Subjects with vitamin D levels below 30 ng/mL at enrollment 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. Vitamin D will be reduced to approximately 1000 IU/day prior to the start of treatment at Visit 2. Repeat laboratory testing for vitamin D is permitted during the enrollment period (up to a maximum of 4 times in 60 days). Investigators should promote compliance by instructing the subject to take the supplements as prescribed and by stating that compliance is important for subject safety.

Vitamin D will be measured and reviewed at each visit. If levels of 25(OH)D fall below 30 ng/mL, supplementation of vitamin D should be increased, as appropriate.

Class effect risks of intravenous aminobisphosphonates that may be associated with neridronic acid

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, 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 moderate to 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), neridronic acid 400 mg will be administered as 4 infusions of neridronic acid 100 mg administered over 240 minutes at Visit 2, Visit 3, Visit 4, and Visit 5.

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).

Medication-related osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) 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 ONJ 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 BMD 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.

Monitoring of changes in serum and urinary calcium may be helpful to predict effects of neridronic acid on bone mineralization, since decreases in these parameters, in the context of a compensatory increase in parathyroid hormone, likely indicate ongoing accretion of calcium into bone (McCloskey et al. 1987).

Additional information relevant for the safety profile

Pregnancy and breastfeeding

There are no adequate and well-controlled trials of neridronic acid in pregnant or lactating women. Although there are no data to suggest a 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 period 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.

Risks related to bone biopsies

Bone biopsies are performed as a minor outpatient surgery and are safe and generally well-tolerated (Kann et al. 2006, Hernandez et al. 2008). Risks include bleeding, hematoma, infection, superficial nerve injury, and pain. Most subjects experience soreness over the biopsy area for 4 days to 5 days. Subjects with increased risk of bleeding (e.g., hemostasis disorders, concomitant treatment with antithrombotic drugs) will be excluded from the bone biopsy assessments.

It is unknown whether a bone biopsy could trigger or worsen CRPS in patients. The limited trials in which bone biopsies were performed in patients with CRPS or similar painful conditions have not suggested that this procedure would be likely to cause severe complications or worsening of CRPS, even when performed in a CRPS-affected region. Since biopsies will be performed only in a region

free of CRPS-related signs and symptoms, this is likely to mitigate the risk of worsening of the condition.

Side effects from tetracycline are rare, but may include skin rashes, photosensitivity, nausea and diarrhea. Women of child-bearing potential using oral contraceptives will be excluded due to potential risk that tetracycline may diminish contraceptive efficacy. Subjects with known allergy to tetracyclines will also be excluded.

Risks related to bone densitometry and magnetic resonance imaging

Bone densitometry using DXA is safe and well tolerated; radiation doses are very low (<5 µSv), generally 10-fold lower than a chest x-ray and 20-fold lower than a standard dental x-ray procedure.

Risks of MRI are due to metallic implants or other ferromagnetic foreign bodies that may be displaced and accelerated toward the magnet, causing tissue damage. Tattoos and cosmetics may contain particles of iron oxide or other metals and may cause burns or local irritation during MRI procedures. Claustrophobic reactions can occur. Ionizing radiation is not involved.

The investigator will assess the appropriateness of the subject for inclusion in the imaging subset and discuss the risks with the subject during the consenting process.

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).

Glass particle contamination may occur when opening ampules, which has the potential to cause harm if injected into the body. Particles of glass or other materials can cause blockages of small vessels and cause damage to internal organs. To reduce the risk of injection of glass particles from broken ampules, sites will receive training information on safe handling of glass ampules. The IMP will be withdrawn from ampules using a filter needle, which should prevent injection of any glass particles.

Blood sampling may cause pain or bruise at the site where the blood is taken due to insertion of the needle. Apart from the bone biopsies from a subset of subjects, 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 Food and Drug Administration (FDA) approved 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 safety as well as efficacy 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 CRPS 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, while 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

	Discontinuation from trial	
Reason	**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

9.3.2 Subject discontinuation from the IMP

Discontinuation of IMP applies only to the treatment period. Subjects who are discontinued from IMP should not be discontinued from the trial except for the 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 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, the treatment period may be extended to a maximum of 21 days (i.e., Visit 5 should occur no later than 21 days after Visit 2). Visit 6 will be scheduled to occur 4 days (±2 days) after Visit 5, but all subsequent visits should occur as originally scheduled relative to Visit 2 (e.g., Visit 7 will be 42 days [6 weeks] after Visit 2). No more than 4 infusions may be administered during the treatment period, and a minimum of 48 hours between any 2 infusions is required.

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

	Discontinuation from IMP	
Reason	**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
Evidence suggestive of a possible change in renal function:		
• A persistent ≥25% decrease from baseline (last value observed prior to treatment) in the eGFR, based on repeated central laboratory results from blood samples obtained at least 1 week apart [a].	X	
• A ≥25% decrease from baseline in the eGFR. If a repeated measurement of eGFR is within 75% or more of the baseline value, the subject may resume treatment [a].		X
• A persistent urinary ACR >300 mg/g based on quantitative urinary albumin and creatinine data from the central laboratory, with urine samples obtained at least 1 week apart.	X	
• 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.		X
• A persistent eGFR <50 mL/min/1.73 m^2 and urinary ACR >150 mg/g based on repeated quantitative data from the central laboratory, with blood and urine samples obtained at least 1 week apart.	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]		
• Resolution of signs and symptoms within 5 days.		X
• Persistent or recurrent signs and symptoms.	X	

	Discontinuation from IMP	
Reason	**Permanent**	**Temporary**
At any point during the treatment period if further assessment may be helpful to assure safety of the subject.		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 prohibited 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) Baseline values of eGFR are obtained from central laboratory results after Visit 2 (based on the blood sample taken at Visit 2 prior to the first administration of IMP). Evaluation of change from baseline in eGFR must occur prior to Visit 4 and Visit 5, based on assessment of central laboratory results from blood samples taken prior to Visit 3 and Visit 4, respectively.

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.

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 CRF.
- Complete activities related to discharge of the subject 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 11. 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 at approximately 4 days after the last infusion, if possible; Visit 7 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, or in response to a recommendation by the independent DMC.
- Decision by the sponsor to terminate the program or for other strategic reasons.

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 product

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.

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

10.1.2 Preparation

The first batch of IMP will be provided to sites in the US in glass ampules and must be removed using a filter needle (to remove any possible glass particles). Instructions will be provided for proper handling of ampules and filter needles. Subsequent batches of IMP will be supplied in vials, which do not require the use of filter needles. Instructions will be provided for the proper handling of vials.

Sites in the EU will receive all batches of IMP in glass 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, United States Pharmacopeia (USP) grade saline for injection) to a volume of approximately 500 mL. 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 CRF.

10.1.3 Packaging and labeling

The IMP will be supplied in kits consisting of either 4 ampules (initially for US sites) or 4 vials (US and EU sites) of IMP. A single kit will be used for each trial subject (i.e., subjects will not receive a mixture of ampules and vials). Ampules or vials are labeled according to each infusion visit (Visit 2 [Day 1], Visit 3 [Day 4], Visit 4 [Day 7], and Visit 5 [Day 10]).

Replacement kits will be available in the event of broken ampules/vials or mishandling during the transfer process that raises concerns for potential contamination.

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

10.1.4 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 product

The full contents of a single ampule or 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 neridronic acid 400 mg. The complete solution volume of 500 ± 50 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 CRF. No more than 4 infusions (400 mg total dose) may be administered to any subject in the trial.

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 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)

Subjects will be assigned to an IMP kit in sequential order using an interactive response technology (IRT) system.

10.4 Blinding and unblinding

Not applicable as this is an open trial.

10.5 Other medication

Name:	Tetracycline hydrochloride.
Active component:	Tetracycline.
Dose (strength):	Tetracycline hydrochloride 250 mg capsules for oral administration.
Supplier:	Grünenthal GmbH, Aachen, Germany.

Tetracycline hydrochloride is applicable only for the subset of subjects at US sites undergoing the bone biopsy.

Further details regarding administration are provided in Section 12.3.8.

10.6 Allowed and forbidden prior/concomitant medications or therapies

Information on allowed or forbidden prior/concomitant medications or therapies is provided in Section 1.4.3.

Recommendations for supplementation of calcium and vitamin D and use of acetaminophen for alleviating symptoms of the acute phase reaction are provided in Section 8.2.

For the purposes of data reporting by the site, the cut-off 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.

10.7 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 IMP. 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 IMP(s) 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 IMP(s), and the administration/intake as documented in the CRF, 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 1.6 for a tabular schedule of events.

11.1 Course of the trial

All visits, except Visit 1, should be attended in a fasting state (at least 8 hours). A non-fasting state does not constitute a protocol deviation.

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

11.1.1 Enrollment period

The general suitability of the subjects for the trial will be assessed during the enrollment period.

Baseline imaging assessments must be scheduled during the enrollment period for subjects who consent to participate in bone imaging assessments (DXA and MRI).

Additional visits are allowed during the enrollment period to confirm normalization of safety laboratory values (e.g., for subjects with vitamin D deficiency).

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.

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

The following evaluations will be performed:

- Obtain written informed consent.
- Record demographic data.
- Record medical history (includes history of CRPS; for further details, see Section 1.6).
- The diagnosis of CRPS must be confirmed using the tablet computer at Visit 1 according to the clinical diagnostic criteria recommended by the IASP (Budapest clinical criteria) (for further details, see Section 12.2.3.1).
- Record dental history (for further details, see Section 1.6).
- Dispense calcium and vitamin D supplements (for further details, see Section 1.6).
- Record prior medications and therapies.
- Review inclusion/exclusion criteria.
- Record physical examination outcome.
- Record vital signs.
- Record triplicate 12-lead ECG.
- Record concomitant medications and therapies.
- Ask the subject to complete pain intensity assessments.
- Take blood for safety laboratory.
- Collect urine for central safety laboratory urinalysis.
- Perform a urine ß-HCG pregnancy test (for women of child-bearing potential).
- Perform urine drugs of abuse testing.
- Provide subject trial card.
- Perform bone imaging (DXA and MRI will be performed in a subset of approximately 30 subjects [from US sites only]).
- Record adverse events (any events noted should be documented as medical history or as part of physical examination results).

11.1.2 Treatment period

The target dosing schedule is Day 1, Day 4, Day 7, and Day 10. Flexibility of ±1 day is allowed for Day 4, Day 7, and Day 10, keeping the overall duration of the infusions within the 10-day period (11 days if Day 10 +1 day). A minimum period of 48 hours is required between infusions.

Central safety laboratory data from the previous visit, in particular eGFR, must be evaluated prior to each infusion.

See Section 9.3.2 for details of temporary suspension of IMP.

Due to the number of procedures and assessments at the infusion visits, subjects should arrive at the site at least 1 hour to 2 hours prior to the start of the infusion; subjects will remain at the center for 1 hour after the end of the infusion for evaluation.

11.1.2.1 Visit 2 (Day 1)

The following evaluations will be performed:

- Review inclusion/exclusion criteria.
- Check subject discontinuation criteria.
- Check IMP suspension criteria (for further details, see Section 9.3.2).
- Record physical examination outcome (changes from the previous visit).
- Record vital signs (once at least 15 minutes before the infusion and once at least 15 minutes after the infusion).
- Record triplicate 12-lead ECG (once at least 15 minutes before the infusion and once at least 15 minutes after the infusion).
- Perform continuous real-time ECG monitoring (for details, see Section 12.3.4).
- Record concomitant medications and therapies.
- Ask the subject to complete pain intensity assessments.
- Ask the subject to complete the BPI interference scale.
- Ask the subject to complete the PDI.
- Ask the subject to complete the EQ-5D-5L.
- Ask the subject to complete the PASS.
- Ask the subject to complete the CES-D.
- Ask the subject to complete the WPAI: CRPS (US sites only).
- Collect medical resources utilization and health economics data (US sites only).
- Complete the assessment of the signs and symptoms of CRPS.
- Take blood for safety laboratory.
- Collect urine for central safety laboratory urinalysis and local dipstick evaluation (calculate urinary ACR).
- Take blood (in the morning) for bone turnover marker evaluation.
- Perform a urine ß-HCG pregnancy test (for women of child-bearing potential).
- Record adverse events (based on subject reporting before, during, and after infusion).
- Allocate to IMP (using IRT system).
- Administer IMP (for further details, see Section 10.2).

11.1.2.2 Visit 3 (Day 4; ±1 day)

The following evaluations will be performed:

- Check subject discontinuation criteria.
- Check IMP suspension criteria (for further details, see Section 9.3.2).

- Record vital signs (once at least 15 minutes before the infusion and once at least 15 minutes after the infusion).
- Record triplicate 12-lead ECG (once at least 15 minutes before the infusion and once at least 15 minutes after the infusion).
- Perform continuous real-time ECG monitoring (for details, see Section 12.3.4).
- Record concomitant medications and therapies.
- Ask the subject to complete pain intensity assessments.
- Take blood for safety laboratory.
- Collect urine for central safety laboratory urinalysis and local dipstick evaluation (calculate urinary ACR).
- Perform a urine ß-HCG pregnancy test (for women of child-bearing potential).
- Record adverse events.
- Administer IMP (for further details, see Section 10.2).

11.1.2.3 Visit 4 (Day 7; ±1 day)

The following evaluations will be performed:

- Check subject discontinuation criteria.
- Check IMP suspension criteria (for further details, see Section 9.3.2).
- Record vital signs (once at least 15 minutes before the infusion and once at least 15 minutes after the infusion).
- Record triplicate 12-lead ECG (once at least 15 minutes before the infusion and once at least 15 minutes after the infusion).
- Perform continuous real-time ECG monitoring (for details, see Section 12.3.4).
- Record concomitant medications and therapies.
- Ask the subject to complete pain intensity assessments.
- Take blood for safety laboratory.
- Collect urine for central safety laboratory urinalysis and local dipstick evaluation (calculate urinary ACR).
- Perform a urine ß-HCG pregnancy test (for women of child-bearing potential).
- Record adverse events.
- Administer IMP (for further details, see Section 10.2).

11.1.2.4 Visit 5 (Day 10; ±1 day)

The following evaluations will be performed:

- Check subject discontinuation criteria.
- Check IMP suspension criteria (for further details, see Section 9.3.2).
- Record vital signs (once at least 15 minutes before the infusion and once at least 15 minutes after the infusion).

- Record triplicate 12-lead ECG (once at least 15 minutes before the infusion and once at least 15 minutes after the infusion).
- Perform continuous real-time ECG monitoring (for details, see Section 12.3.4).
- Record concomitant medications and therapies.
- Ask the subject to complete pain intensity assessments.
- Take blood for safety laboratory.
- Collect urine for central safety laboratory urinalysis and local dipstick evaluation (calculate urinary ACR).
- Perform a urine ß-HCG pregnancy test (for women of child-bearing potential).
- Record adverse events.
- Administer IMP (for further details, see Section 10.2).

11.1.3 Follow-up period

11.1.3.1 Visit 6 (Week 2; ±2 days)

The following evaluations will be performed:

- Check subject discontinuation criteria.
- Record vital signs.
- Record triplicate 12-lead ECG.
- Record concomitant medications and therapies.
- Ask the subject to complete pain intensity assessments.
- Take blood for safety laboratory.
- Collect urine for central safety laboratory urinalysis.
- Take blood (in the morning) for bone turnover marker evaluation.
- Record adverse events.

11.1.3.2 Visit 7 (Week 6; ±7 days)

The following evaluations will be performed:

- Check subject discontinuation criteria.
- Record vital signs.
- Record concomitant medications and therapies.
- Ask the subject to complete pain intensity assessments.
- Ask the subject to complete the PGIC.
- Ask the subject to complete the BPI interference scale.
- Ask the subject to complete the PDI.
- Ask the subject to complete the EQ-5D-5L.
- Ask the subject to complete the PASS.
- Ask the subject to complete the CES-D.
- Complete the assessment of the signs and symptoms of CRPS.

- Take blood for safety laboratory.
- Collect urine for central safety laboratory urinalysis.
- Take blood (in the morning) for bone turnover marker evaluation.
- Record adverse events.

11.1.3.3 Visit 8 (Week 12; ±7 days)

The following evaluations will be performed:

- Check subject discontinuation criteria.
- Record physical examination outcome (changes from the previous visit).
- Record vital signs.
- Record concomitant medications and therapies.
- Ask the subject to complete pain intensity assessments.
- Ask the subject to complete the PGIC.
- Ask the subject to complete the BPI interference scale.
- Ask the subject to complete the PDI.
- Ask the subject to complete the EQ-5D-5L.
- Ask the subject to complete the PASS.
- Ask the subject to complete the CES-D.
- Complete the assessment of the signs and symptoms of CRPS.
- Take blood for safety laboratory.
- Collect urine for central safety laboratory urinalysis.
- Take blood (in the morning) for bone turnover marker evaluation.
- Record adverse events.
- Prescribe tetracycline and dispense tetracycline dosing diary to US subjects undergoing a bone biopsy for recording the intake of tetracycline.

11.1.3.4 Visit 9 (Week 26; ±15 days)

A single bone biopsy will be obtained from the iliac crest, following tetracycline double-labeling, in a subset of subjects (from US sites only). The biopsy should be scheduled to be performed 26 weeks after the first administration of IMP. Biopsies will be obtained from approximately 20 subjects to obtain approximately 15 evaluable biopsy specimens.

The following evaluations will be performed:

- Check subject discontinuation criteria.
- Record physical examination outcome (changes from the previous visit).
- Record vital signs.
- Record triplicate 12-lead ECG.
- Record concomitant medications and therapies.
- Ask the subject to complete pain intensity assessments.

- Ask the subject to complete the PGIC.
- Ask the subject to complete the BPI interference scale.
- Ask the subject to complete the PDI.
- Ask the subject to complete the EQ-5D-5L.
- Ask the subject to complete the PASS.
- Ask the subject to complete the CES-D.
- Ask the subject to complete the WPAI: CRPS (US sites only).
- Collect medical resources utilization and health economics data (US sites only).
- Complete the assessment of the signs and symptoms of CRPS.
- Take blood for safety laboratory.
- Collect urine for central safety laboratory urinalysis.
- Take blood (in the morning) for bone turnover marker evaluation.
- For women of child-bearing potential allocated to treatment after the first 100 subjects have been allocated, perform a urine ß-HCG pregnancy test.
- For all subjects allocated to treatment after the first 100 subjects have been allocated, collect subject trial card.
- Perform bone imaging (DXA and MRI will be performed in a subset of approximately 30 subjects [from US sites only]).
- Record adverse events.
- Collect tetracycline dosing diary from US subjects undergoing a bone biopsy.

11.1.3.5 Visit 10 (Week 39; ±15 days)

The following evaluations will be performed:

- Check subject discontinuation criteria.
- Record physical examination outcome (changes from the previous visit).
- Record vital signs.
- Record concomitant medications and therapies.
- Ask the subject to complete pain intensity assessments.
- Ask the subject to complete the PGIC.
- Ask the subject to complete the BPI interference scale.
- Ask the subject to complete the PDI.
- Ask the subject to complete the EQ-5D-5L.
- Ask the subject to complete the PASS.
- Ask the subject to complete the CES-D.
- Complete the assessment of the signs and symptoms of CRPS.
- Take blood for safety laboratory.
- Collect urine for central safety laboratory urinalysis.
- Take blood (in the morning) for bone turnover marker evaluation.

- Record adverse events.

11.1.3.6 Visit 11 (Week 52; ±15 days)

The following evaluations will be performed:

- Record physical examination outcome (changes from the previous visit).
- Record vital signs.
- Record triplicate 12-lead ECG.
- Record concomitant medications and therapies.
- Ask the subject to complete pain intensity assessments.
- Ask the subject to complete the PGIC.
- Ask the subject to complete the BPI interference scale.
- Ask the subject to complete the PDI.
- Ask the subject to complete the EQ-5D-5L.
- Ask the subject to complete the PASS.
- Ask the subject to complete the CES-D.
- Ask the subject to complete the WPAI: CRPS (US sites only).
- Collect medical resources utilization and health economics data (US sites only).
- Complete the assessment of the signs and symptoms of CRPS.
- Take blood for safety laboratory.
- Collect urine for central safety laboratory urinalysis.
- Take blood (in the morning) for bone turnover marker evaluation.
- Perform a urine ß-HCG pregnancy test (for women of child-bearing potential).
- Collect subject trial card.
- Record adverse events.

11.2 Examination hierarchy and time windows

Electrocardiograms should be taken before invasive procedures. When practical, blood samples for safety laboratory evaluation should be taken after all non-invasive procedures (including completion of questionnaires) have been finished. During the Treatment Period, procedures should be performed prior to administration of IMP, except where indicated.

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

Blood samples for bone turnover markers should be obtained in the morning after an overnight fast (at least 8 hours) at Visit 2 and at Visits 6, 7, 8, 9, 10, and 11.

Light meals are allowed after sampling for blood turnover markers and may be provided before and/or after IMP infusions at Visit 2, Visit 3, Visit 4, and Visit 5.

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

Subjects undergoing bone biopsy should cease calcium supplements and avoid milk and dairy products during administration of tetracycline.

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 1.6). 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.

The card will be collected at the last visit.

11.5 Provisions of any additional care of subject after trial termination

Subjects will be encouraged to continue daily calcium and vitamin D supplementation for 1 year from the start of treatment.

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 is estimated to be less than 180 mL during the trial (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). The volume of blood taken may vary due to trial site requirements.

Sampling times are given in the schedule of events (Section 1.6).

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

Test	Unit volume of blood	Number of samples	Total
Sampling for bone turnover markers	7.5 mL	7	52.5 mL
Sampling for central safety laboratory monitoring:			
Hematology	3 mL	11	33 mL
Clinical chemistry [a]	5 mL	11	55 mL
Parathyroid hormone	3 mL	11	33 mL
Total		**40**	**173.5 mL**

The volume of blood taken may be individually variable due to local practices and the potential need for resampling.
a) Includes vitamin D testing.

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, and height.

Body weight and body mass index will be determined at all trial visits and are listed with vital signs instead of demographic data (Section 12.3.2).

12.2.2 Prior and concomitant medication or therapies

All medication requiring prescriptions (including oral contraceptives), over-the-counter medication, and therapies used within 3 months prior to enrollment and up to the end of the trial must be recorded in the CRF. Any change in dosage, regimen, or route, must be recorded in the CRF as a new entry.

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 CRF (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 CRF.

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 (especially hand or foot), with or without proximal spread, should 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 CRF. 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. **Diagnosis of CRPS involving an atypical body part (e.g., trunk, breasts, pelvic regions, lower back, face) 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 active range of motion, or weakness) (see Section 18.4).

Medical history related to CRPS must include the following: date and description of precipitating event (e.g., type of trauma, surgery; 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, and date of CRPS diagnosis. 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 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 predispose to risk of medication-related ONJ.

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 the Enrollment Visit 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 CRF:

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

Subjects who are receiving stable doses of prescribed medications containing amphetamines, benzodiazepines, or opioids may participate (according to the judgment of the investigator upon approval by the sponsor) even if the test is positive.

12.3 Collection of safety data

The following safety data will be collected: adverse events, vital signs, 12-lead ECGs, safety laboratory parameters, physical examination findings, urine ß-HCG pregnancy test outcome, and bone biopsies for histology and histomorphometry (in a subset of subjects).

For the timings of assessments, see the schedule of events (Section 1.6).

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

12.3.1 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 1.6.

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

All adverse events will be documented in the CRF 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 IMP(s).

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.

12.3.2 Vital signs

The vital signs comprise systolic and diastolic blood pressure, pulse rate, respiratory rate, body weight and body mass index.

Body weight will be measured in light clothes.

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.

12.3.3 Twelve-lead electrocardiogram

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

Electrocardiogram parameters will include heart rate and the following ECG intervals (measured or derived); QRS, PR, RR, QT, corrected QT interval (to Bazett's formula; QTcB), and QTcF. The ECG central reader will provide an assessment and interpretation of any waveform abnormalities and other findings (e.g., conduction defects). Both the locally obtained ECG and the report from the ECG central reader must be reviewed by the investigator; the investigator will be responsible for determining the clinical significance of any abnormality. Results will be documented by the investigator as "normal", "abnormal, clinically not relevant", or "abnormal, clinically relevant".

For decisions pertaining to subject exclusion or discontinuation of IMP due to QT prolongation, the average QTcF, calculated from 3 successive ECGs, will be used. Values from the ECG central reader will supersede interval values reported by the ECG machine.

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

The original ECG recordings will be kept at the site.

12.3.4 Continuous real-time ECG monitoring

Continuous real-time ECG monitoring, which may be performed by telemetry, will be performed at the infusion visits (Day 1, Day 4, Day 7, and Day 10), starting at least 30 minutes prior to the beginning of each infusion and for up to at least 30 minutes after the end of each infusion. Continuous real-time ECG monitoring must be performed by a qualified person. Personnel trained in advanced cardiopulmonary resuscitation must be on site and readily available to treat any potential cardiac rhythm disturbances.

Electrocardiogram machines may be used for continuous real-time ECG monitoring.

12.3.5 Safety laboratory

Laboratory tests (except for urine dipsticks for urine drugs of abuse testing and urine pregnancy testing) will be performed by a central safety laboratory. At Visit 2, Visit 3, Visit 4, and Visit 5, in addition to taking blood and urine samples for evaluation at the central safety laboratory, an assessment of urinary ACR will be performed prior to infusion using a semi-quantitative dipstick.

The use of any clinical laboratory facility other than the designated central safety laboratory 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 central safety laboratory before the trial start and is to be filed in the investigators site file.

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

Alert ranges for specific laboratory parameters will be provided by the sponsor to the central safety laboratory. Any laboratory value within these alert ranges will be immediately reported to the investigator.

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

Throughout the clinical part of the trial, the investigator must provide a comment in the CRF regarding the clinical relevance of any laboratory values outside of the sponsor-defined alert range. Any abnormal laboratory result considered clinically relevant will be followed until it reaches a satisfactory resolution, becomes stable, or can be explained by other causes (e.g., concurrent condition or medication), and clinical judgment indicates that further evaluation is not needed. The printout of the laboratory values will be stored with the source data.

Data will be transferred from the central safety laboratory to the sponsor electronically.

The following tests will be performed:

Hematology panel	
Hemoglobin	Mean cell volume (MCV)
Hematocrit	Platelet count
Mean cell hemoglobin (MCH)	Red blood cell (RBC) count
Mean cell hemoglobin concentration (MCHC)	White blood cell (WBC) count with differential count [a]

a) Includes neutrophils, lymphocytes, monocytes, basophils, eosinophils (absolute count and percent).

Clinical chemistry panel	
Alanine aminotransferase (ALT)	Lactic acid dehydrogenase (LDH)
Albumin	Lipase
Alkaline phosphatase	Magnesium
Aspartate aminotransferase (AST)	Parathyroid hormone
Bicarbonate	Phosphorus
Blood urea nitrogen (BUN)	Potassium
Calcium (measured and albumin-corrected)	Sodium
Chloride	Total bilirubin
Cholesterol	Total protein
Creatine phosphokinase	Triglycerides
Creatinine (serum)	Uric acid
Gamma-glutamyl transferase (GGT)	Vitamin D
Glucose	

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

Urinalysis panel	
Dipstick	**Quantitative Analysis**
Albumin creatinine ratio (ACR) [a]	Albumin (microalbumin)
pH	Calcium
Glucose	Creatinine
Urobilinogen	Calculated urinary ACR
Blood (erythrocytes)	
Leukocyte esterase	
Protein	
Ketone	
Bilirubin	
Nitrite	

a) Determined at site on infusion days only.

If the dipstick test is positive (except for glucose or ketones, and blood/leucocytes in menstruating subjects), a microscopic examination of urine sediment will be performed to determine the presence of red blood cells, white blood cells, epithelial cells, crystals, casts, and bacteria.

If either alanine aminotransferase or aspartate aminotransferase are more than 3-fold the upper limit of the central laboratory reference range, the laboratory test should be repeated within 72 hours. If elevated values are confirmed, a standard algorithm to detect and follow up on potential severe cases of drug-induced liver injury will be applied (see Section 18.2).

12.3.6 Physical examination

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

12.3.7 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 ß-HCG pregnancy dipstick test.

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

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

12.3.8 Bone biopsy procedures

Iliac crest bone biopsies will be performed in a subset of trial subjects to assess the bone safety of neridronic acid 400 mg. Bone biopsies will be obtained from subjects participating at sites in the US. Subject eligibility may depend on proximity to clinical facilities where biopsies will be performed. Only a single biopsy will be obtained from each participating subject.

Subjects consenting to bone biopsy will undergo double-tetracycline labeling starting up to 40 days prior to the scheduled biopsy procedure at month 6. Oral tetracycline hydrochloride will be given for an initial 3-day cycle, followed by a 14-day interval without tetracycline, and by a second 3-day cycle of oral tetracycline. The dose of tetracycline will be 250 mg 4 times a day for 3 days. Subjects will be instructed to take each dose 1 hour to 2 hours before a meal or 2 hours after a meal. The subjects are to be instructed to record the intake of tetracycline in a tetracycline dosing diary. Subjects should not take oral calcium supplements on days they are taking tetracycline. If a dose of tetracycline is skipped/missed, it should be taken as soon as possible or with the next scheduled dose, and the information regarding the missed/skipped dose should be entered into the subject's file.

Site staff must phone each subject several times during the scheduled tetracycline dosing in order to ensure good compliance with the dosing schedule. The tetracycline dosing diary will be verified for dosing schedule compliance before performing the iliac crest bone biopsy.

An iliac crest biopsy will be obtained 5 days to 14 days after the last dose of tetracycline according to procedures of Dempster and Shane (1995). Prior to the bone biopsy, subjects may receive optional intravenous sedation. The site of the biopsy will be numbed with a local anesthetic (e.g., xylocaine, lidocaine) to minimize discomfort.

Biopsies will be performed using a Bordier type biopsy needle with a minimum internal diameter of 7.5 mm to ensure an adequate sample size. Evaluable biopsies must contain inner and outer cortical plates with intervening cancellous bone. The biopsy will be performed only by investigators who are skilled and experienced in this procedure. For subjects with lower limb CRPS, the biopsy must be taken from the hip contralateral to the CRPS-affected limb.

Subjects will return to the bone biopsy center 7 days to 10 days after the bone biopsy to have stitches removed.

The following information must be recorded in the CRF:

- Confirmation that informed consent was obtained to perform biopsy.
- Dates of tetracycline dosing and confirmation that the dose was taken.
- Date of biopsy and confirmation that biopsy was taken.

Bone biopsies will be processed for histology and for measurement of static and dynamic histomorphometry according to standard procedures (Recker et al. 2011; Dempster et al. 2013). Qualitative histological analysis will include assessment for evidence of bone mineralization abnormalities (i.e., osteomalacia), woven bone, marrow fibrosis, abnormalities in cellular components, or other abnormalities. Unstained sections will be viewed by fluorescence microscopy and will be used for determination of dynamic histomorphometry parameters using tetracycline-based indices. The tetracycline dosing diary data on tetracycline intake recorded by the subjects will be transferred to the histomorphometry laboratory. Quantitative histomorphometric analysis will include assessment of static parameters (e.g., osteoid thickness, osteoid surface, osteoid volume, and dynamic parameters (e.g., mineral apposition rate, mineralizing surface, bone formation rate, mineralization lag time, osteoid maturation time, and activation frequency); all indices will be calculated and expressed according to the recommendations of the American Society for Bone and Mineral Research (Dempster et al. 2013).

Data from the histomorphometry measurements and standard histologic examination will be transferred electronically to the data management center using a secure method at predefined intervals during the trial.

12.4 Collection of efficacy data

The following efficacy data will be collected: pain intensity, PGIC, BPI interference scale, PDI, EQ-5D-5L, PASS, CES-D, and CRPS Severity Score.

For the timings of assessments, see the schedule of events (Section 1.6).

12.4.1 Pain intensity

Pain intensity assessments will be captured in an electronic patient reported outcome system kept at the sites. Subjects will be asked to record their current, worst, and average CRPS-related pain intensity at each visit using an 11-point NRS (from 0 = “no pain” to 10 = “pain as bad as you can imagine”).

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

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."

Worst pain assessment

Subjects will be asked to record their worst 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 your pain at its worst during the last 24 hours."

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."

12.4.2 Patient Global Impression of Change

The PGIC will be assessed at Visit 7 through Visit 11. 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.

12.4.3 Brief Pain Inventory interference scale

Subjects will complete the BPI Interference Scale questionnaire (Section 18.3.2) at Visit 2 and Visit 7 through Visit 11. This is a multi-item scale measuring the impact of pain on functioning and well-being. The 7 pain interference items: general activity, walking, work, mood, enjoyment of life, relations with others, and sleep, are each rated on a 0 to 10 scale using a 24-hour recall period, with 0 indicating "does not interfere" and 10 indicating "completely interferes". The total Pain Interference Score is calculated by adding the scores for the 7 questions and dividing by 7. This gives an interference score with a range from 0 to 10. This mean can be calculated if more than 50% (four of seven) of the total items have been completed on a given administration. A 1 point decrease in the BPI Interference Scale score is generally considered as the minimum clinically important decrease (Dworkin et al. 2008).

12.4.4 Pain Disability Index

The PDI questionnaire (Section 18.3.3) will be completed by all subjects at Visit 2 and Visit 7 through Visit 11. The PDI questionnaire includes questions related to pain-related disability in 7 categories: family/home responsibilities, recreation, social activity, occupation, sexual behavior,

self-care, and life-support activities. For each of the 7 categories, the subjects are asked to rate on an 11-point NRS the level of disability they typically experience. The PDI is calculated as the sum of the 7 categories, for a minimum value of 0 and maximum value of 70. Higher scores indicate greater disability due to pain. In other chronic pain conditions, a decrease of 8.5 points to 9.5 points in the PDI was considered to be clinically important (Soer et al. 2012).

12.4.5 EuroQoL-5 dimension 5 level

The EQ-5D-5L health questionnaire (Section 18.3.4) will be completed by all subjects at Visit 2 and Visit 7 through Visit 11. 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.

12.4.6 Pain Anxiety Symptom Scale

The PASS questionnaire (Section 18.3.5) will be completed by all subjects at Visit 2 and Visit 7 through Visit 11. The PASS questionnaire consists of 20 items designed to assess 4 aspects of pain-related anxiety: cognitive anxiety, escape-avoidance behaviors, fear of pain, and physiological symptoms of anxiety. Subjects rate each item in terms of frequency, from 0 (never) to 5 (always). The total score is calculated as the sum of ratings, with values ranging from 0 to 100; higher scores indicate higher levels of pain-related anxiety.

12.4.7 Center for Epidemiological Studies Depression Scale

The CES-D questionnaire (Section 18.3.6) will be completed by all subjects at Visit 2 and Visit 7 through Visit 11. The CES-D is a short questionnaire designed to measure depressive symptomatology in the general population. The 20 items of the scale are symptoms associated with depression which have been used in previously validated longer scales. Subjects are asked to rate each item from “rarely or none of the time (less than 1 day)” to “most or all of the time (5 to 7 days)” during the last week. Response scores for all questions except 4, 8, 12, and 16 are: <1 day = 0; 1-2 days = 1; 3-4 days = 2; 5-7 days = 3. For questions 4, 8, 12, and 16, the scoring is reversed. The total CES-D score is calculated as the sum of scores for all 20 questions and has a range of 0 to 60. A score over 21 indicates the possibility of major depression.

12.4.8 CRPS Severity Score

Signs and symptoms of CRPS (Section 18.4) will be assessed by the investigator at Visit 2 (baseline) and Visit 7 through Visit 11 and recorded using the electronic patient reported outcome system. Subjects will be queried on 8 self-reported symptoms (queried yes or no): allodynia and/or hyperalgesia; temperature asymmetry; skin color asymmetry; sweating asymmetry; asymmetric edema; dystrophic changes; motor changes; and decreased active range of motion. 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. 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).

12.5 Collection of pharmacodynamic data

12.5.1 Bone turnover markers

Samples taken for bone turnover marker evaluation should be collected in the morning after an overnight fast (at least 8 hours) due to diurnal variation and effects of a meal. Serum concentrations will be determined for CTX, BAP, and PINP.

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

12.5.2 Bone densitometry and magnetic resonance imaging

Subjects selected from sites in the US for inclusion in the imaging subset must have distal limb involvement (i.e., CRPS signs and symptoms located in the hand, foot, wrist or ankle), with or without proximal spread, as described in Section 12.2.3.1. Distal localization is required due to specific MRI coils intended for selected imaging of wrist/hand and ankle/foot. Subjects with metallic implants or other contraindications to MRI, including claustrophobia reactions, will be excluded.

All imaging will be performed by trained technicians at selected imaging facilities in reasonable proximity to trial sites.

The following information must be recorded in the CRF:

- Confirmation that informed consent was obtained to perform bone imaging.
- Dates of DXA performance (baseline and 6-month assessments).
- Dates of MRI performance (baseline and 6-month assessments).
- Limb/region where DXA and MRI were performed.

Data from the bone imaging assessments will be transferred electronically to the data management center using a secure method at predefined intervals during the trial.

Bone densitometry

Dual energy x-ray absorptiometry of the CRPS-affected limb, contralateral (unaffected) limb, and lumbar spine. The same DXA machine must be used for baseline and 6-month scans for a particular subject. Lumbar spine scans will include L1 through L4. DXA scans will be submitted to and analyzed by the central imaging vendor. A manual will be provided by the central imaging vendor with specific instructions for acquisition of scans as well as performance of instrument quality control.

Bone mineral content and bone area will be used to determine areal BMD in the CRPS-affected limb, contralateral limb and lumbar spine. T scores will be determined for the lumbar spine. Change Pattern analysis will be performed comparing ROIs from the CRPS-affected and contralateral extremities. The principal outcome measure for this analysis will be change from baseline in areal BMD of ROIs in the CRPS-affected limb, relative to the contralateral limb.

Magnetic resonance imaging

High-resolution, three-dimensional MRI will be performed at baseline (during the enrollment period) and approximately 6 months after the start of treatment. Magnetic resonance imaging will be performed using 1.5 or 3 Tesla MRI instrument at facilities in reasonable proximity to trial sites. T1 and T2-weighted images will be acquired of the CRPS-affected and contralateral limbs. No gadolinium contrast agent will be used. Imaging will be performed on sagittal, coronal, and transverse planes, with appropriate field of view to encompass the CRPS-affected limb. Bone marrow lesions will be identified as areas of increased signal intensity on fat-suppressed T2-weighted images. Volume of all bone marrow lesions in the CRPS-affected and contralateral limb will be determined by a radiologist or appropriately trained technician who is blinded to the affected limb and treatment sequence (pre- or post-treatment). Pattern analysis will be performed comparing ROIs from the CRPS-affected and contralateral extremities. The outcome measure will be change from baseline in total volume of bone marrow lesions in the CRPS-affected limb, relative to the contralateral limb.

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

12.6.1 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 18.3.7).

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 at Visit 2, at Week 26, and at Week 52.

12.6.2 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 Visit 2, at Visit 9, and at Week 52.

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 CRF by the investigator.

12.7 Appropriateness of measurements

As CRPS is a rare, poorly understood chronic pain syndrome condition with very few adequate and well-controlled trials having been conducted, none of the proposed outcome measures for this trial have been formally validated in this population. Consequently, outcome measures selected for this trial were based on clinical outcome measures used in interventional trials in more common chronic pain conditions.

Safety assessments

Bone histology and histomorphometry

Bone histology and histomorphometry, performed on transiliac bone biopsy specimens, are established and standardized procedures to assess for the presence of bone abnormalities such as osteomalacia (Dempster et al. 2013). Clinical evaluation of bone histology and histomorphometry is required by the FDA for evaluation of the safety of new drugs and biologic products for treatment of osteoporosis, including bisphosphonates. Effects of neridronic acid on bone histology and histomorphometry was previously evaluated in biopsies from 14 patients with Paget's disease receiving neridronic acid 250 mg (50 mg/day for 5 days; McCloskey et al. 1987; Atkins et al 1987). Neridronic acid improved indices of bone turnover in pagetic bone, and normal bone mineralization and bone formation were observed in biopsies from healthy, non-pagetic bone in the iliac crest.

Efficacy assessments

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 the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (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). Current, average and worst pain intensity will be assessed, with average and worst pain assessed using a 24-hour recall.

An electronic subject-reported outcome will be used to ensure data integrity by only allowing subjects to access the tool. Electronic diaries 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).

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).

Brief Pain Inventory interference scale

The BPI interference scale shows reliability and validity for chronic pain and is a core outcome measure for the assessment of the impact of chronic pain on activities of daily living (Dworkin et al. 2005).

Pain Disability Index

The PDI is a brief instrument that was developed to assess pain-related disability, providing information that complements the assessment of physical impairment.

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.

Pain Anxiety Symptom Scale

The 20-item PASS, based on the original 40-item PASS, was developed by McCracken and Dhingra (2002) to assess anxiety related specifically to pain in clinical and research contexts. It shows strong internal consistency, reliability, and good predictive and construct validity.

Center for Epidemiological Studies Depression Scale

The CES-D scale was tested in household interview surveys and in psychiatric settings. It was found to have very high internal consistency and adequate test-retest repeatability. Validity was established by patterns of correlations with other self-report measures, by correlations with clinical ratings of depression, and by relationships with other variables which support its construct validity. Reliability, validity, and factor structure were similar across a wide variety of demographic characteristics in the general population samples tested (Radloff 1977).

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.

Bone densitometry and magnetic resonance imaging

Bone abnormalities, including regional osteoporosis/osteopenia on X-rays and osteolytic lesions identified by uptake of radiolabelled bisphosphonate and triple-phase bone scintigraphy, have been described in patients with CRPS (O'Donoghue et al. 1993; Veldman et al 1993; Wüppenhorst et al. 2010; Ringer et al. 2012). In addition, bone marrow lesions, defined as ill-defined areas of hyperintense signal intensity on T2- or intermediate-weighted fat-suppressed and short-tau inversion recovery magnetic resonance images, have also been reported in CRPS (Crozier et al. 2003, Varenna et al. 2013) and are thought to overlap with regions of high bone turnover.

Dual-energy X-ray absorptiometry and MRI are established, noninvasive imaging methods that have been used extensively in trials investigating bisphosphonates for treatment of osteoporosis, osteoarthritis, and other conditions.

Medical resources utilization and health economics data collection

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, and Crohn's disease. 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.

12.8 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 will be ensured by capturing the information in an electronic patient reported outcome system at the sites.

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 CRFs to record information required by the protocol.

All CRF 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 CRF system. The collected data will reside on servers of the CRF 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 subjects CRF, the CRF must be signed electronically by the investigator. With the investigator's signature it is confirmed that the data in the CRF are checked, complete, accurate, and in alignment with the source data. Changes to the CRF after initial signing by the investigator need re-signing.

With database lock, the edit rights to the CRFs will be removed but the investigator will retain access to view the CRFs 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.

13.1.1 Subject tetracycline dosing diary

A subject tetracycline dosing diary will be used to record the intake of tetracycline in US subjects undergoing a transiliac bone biopsy. These data will be supplied to the histomorphometry laboratory for incorporation into the bone biopsy record.

13.2 Subject reported outcomes

Subject reported outcomes will be collected using a validated electronic patient reported outcome system including audit trail.

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.

The electronic patient reported outcome 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 CRF or subject reported outcome, but requested per protocol (e.g., safety laboratory data, ECG data, bone biopsy data, bone imaging 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 CRF and not in other documents. When this occurs, the CRF is considered to be the source document. Data expected to be only recorded in the CRF 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 CRF 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.

Subset of subjects for bone biopsies

The sample size is not based on statistical considerations; bone biopsy specimen evaluation will identify qualitative bone abnormalities such as osteomalacia as well as quantitative indicators of impaired mineralization.

Subset of subjects for bone densitometry and magnetic resonance imaging

The sample size is not selected based on statistical considerations. Results from this subset of subjects are considered to be sufficient to demonstrate feasibility and explore outcomes of these assessments in trials of neridronic acid in CRPS.

14.1.2 General description of statistical analyses

The statistical analysis of this trial will be performed as described and summarized in the protocol. Full details of the planned statistical analyses will be described in the trial statistical analysis plan.

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

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

Collected and derived data will be listed.

Summary statistics and graphical methods will be used to describe parameters/variables.

The following descriptive statistics will be produced on the basis of the nature of the relevant variable:

- For continuous variables: number of non-missing observations, arithmetic mean, standard deviations, minimum, first quartile, median, third quartile, and maximum.
- For categorical variables: absolute and relative frequencies and percentages.

14.1.3 Analysis populations (analysis sets)

The analysis populations are defined in 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

Demographic data, baseline characteristics, medical history, concomitant medications, and exposure will be summarized descriptively for the Safety Set.

14.1.6 Analysis of safety data

14.1.6.1 Adverse events

A definition of adverse event is given in Section 12.3.1.

The original terms recorded in the CRF 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.

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 period are also considered TEAEs.

Treatment emergent adverse events will be summarized for each treatment group by System Organ Class and Preferred Term. Additional summaries by time to onset, duration, intensity, relationship to the IMP, outcome, expectedness, and countermeasures will also be created. To account for the differences in the planned trial duration of the subjects in this trial, an analysis of exposure-adjusted incidence rates will be done in addition to the analysis of crude incidence rates.

Subjects with SAEs will be summarized and additionally listed. Special attention will be given to those subjects who discontinue treatment due to an adverse event or who experience a severe or SAE.

The incidences and incidence rates of all adverse events will be summarized descriptively.

Permanent discontinuations from treatment due to adverse events will be summarized descriptively.

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

14.1.6.1.1 Analysis of the primary endpoint

The primary endpoint of this trial is a binary endpoint assessing whether or not a subject experienced any TEAE.

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

Safety laboratory values, vital signs, and 12-lead ECG will be summarized descriptively.

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

Sponsor-defined alert ranges will be defined for selected parameters. Subjects with values outside of sponsor-defined alert ranges will be summarized. Subjects with abnormal values will be tabulated and listed separately.

14.1.6.3 Bone biopsy assessments

The occurrence of histomorphometric evidence of osteomalacia, defined as osteoid thickness >12.5 µm (corrected for obliquity) and mineralization lag time >100 days (Dempster et al. 2013) will be derived for each assessed subject. All bone biopsy parameters will be descriptively summarized for the Bone Biopsy Set.

14.1.7 Analysis of efficacy data

The analysis of all efficacy endpoints will be exploratory and will be summarized using descriptive statistics unless stated otherwise. Analyses will be performed on all post baseline measurements.

Handling of missing data

Missing data will not be imputed in this trial. The number of missing data will be included in all descriptive summaries.

An MMRM will be conducted on the observed values of the change in current pain intensity score. An MMRM leads to unbiased estimates if the missingness mechanism is missing-at-random. Due to the long-acting effect of neridronic acid, missing-at-random is considered a clinically plausible assumption. The MMRM in this trial will include the covariate baseline pain intensity and the factors pooled site and visit as fixed effects, and subject as random effect. An unstructured covariance matrix will be used to model the covariance structure. Least squares means, standard errors, and 95% confidence intervals for the change from baseline will be obtained.

14.1.8 Analysis of pharmacodynamic data

Bone turnover markers including changes from baseline will be descriptively summarized for the Pharmacodynamic Set. Baseline is defined by the value on Day 1 (Visit 2).

14.1.9 Analysis of bone imaging data

Bone densitometry and magnetic resonance imaging parameters including changes from baseline will be descriptively summarized for the Bone Imaging Set. Baseline is defined by the value at Visit 1.

14.1.10 Analysis of health economics outcome and work productivity data

Medical resources utilization and health economics data will be descriptively summarized.

14.1.11 Interim analysis

Not applicable.

14.1.12 Ad hoc meta-analyses

Data collected in this trial may be used for ad hoc meta-analyses. These meta-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 investigators, 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 site(s) 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 should 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 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 unless it can be shown to affect possible patent rights.

16.6 Trial results reporting

A final report integrating clinical, pharmacodynamics 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.

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

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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 lymphoprolipherative 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: Jul 2012

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)

PGIC - USA/English – Original version

18.3.2 Brief Pain Inventory interference scale

Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

18.3.3 Pain Disability Index

Pain Disability Index

Pain Disability Index: The rating scales below are designed to measure the degree to which aspects of your life are disrupted by chronic pain. In other words, we would like to know how much pain is preventing you from doing what you would normally do or from doing it as well as you normally would. Respond to each category indicating the overall impact of pain in your life, not just when pain is at its worst.

For each of the 7 categories of life activity listed, please circle the number on the scale that describes the level of disability you typically experience. A score of 0 means no disability at all, and a score of 10 signifies that all of the activities in which you would normally be involved have been totally disrupted or prevented by your pain.

Family/Home Responsibilities: This category refers to activities of the home or family. It includes chores or duties performed around the house (e.g. yard work) and errands or favors for other family members (e.g. driving the children to school).

No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Total Disability

Recreation: This category includes hobbies, sports, and other similar leisure time activities.

No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Total Disability

Social Activity: This category refers to activities, which involve participation with friends and acquaintances other than family members. It includes parties, theater, concerts, dining out, and other social functions.

No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Total Disability

Occupation: This category refers to activities that are part of or directly related to one's job. This includes non-paying jobs as well, such as that of a housewife or volunteer.

No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Total Disability

Sexual Behavior: This category refers to the frequency and quality of one's sex life.

No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Total Disability

Self Care: This category includes activities, which involve personal maintenance and independent daily living (e.g. taking a shower, driving, getting dressed, etc.)

No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Total Disability

Life-Support Activities: This category refers to basic life supporting behaviors such as eating, sleeping and breathing.

No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Total Disability

Signature_____ **Please Print**_____

Date _____

18.3.4 EuroQol-5 dimension 5 level

DMS version: 1.0 ID: 1028200

EQ-5D-5L

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

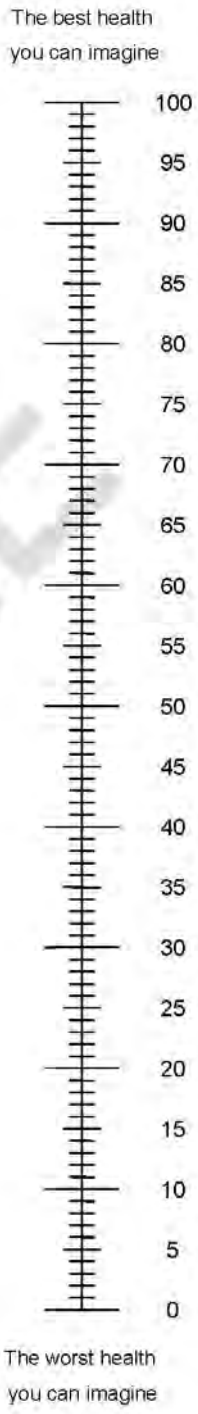
- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

2

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 = ☐



18.3.5 Pain Anxiety Symptom Scale

PASS

Individuals who experience pain develop different ways to respond to that pain. We would like to know what you do and what you think about when in pain. Please use the rating scale below to indicate how often you engage in each of the following thoughts or activities. Circle any number from 0 (NEVER) to 5 (ALWAYS) for each item.

		NEVER					ALWAYS
1.	I think that if my pain gets too severe, it will never decrease	0	1	2	3	4	5
2.	When I feel pain I am afraid that something terrible will happen	0	1	2	3	4	5
3.	I go immediately to bed when I feel severe pain	0	1	2	3	4	5
4.	I begin trembling when engaged in activity that increases pain	0	1	2	3	4	5
5.	I can't think straight when I am in pain	0	1	2	3	4	5
6.	I will stop any activity as soon as I sense pain coming on	0	1	2	3	4	5
7.	Pain seems to cause my heart to pound or race	0	1	2	3	4	5
8.	As soon as pain comes on I take medication to reduce it	0	1	2	3	4	5
9.	When I feel pain I think that I may be seriously ill	0	1	2	3	4	5
10.	During painful episodes it is difficult for me to think of anything else besides the pain	0	1	2	3	4	5
11.	I avoid important activities when I hurt	0	1	2	3	4	5
12.	When I sense pain I feel dizzy or faint	0	1	2	3	4	5
13.	Pain sensations are terrifying	0	1	2	3	4	5
14.	When I hurt I think about the pain constantly	0	1	2	3	4	5
15.	Pain makes me nauseous (feel sick)	0	1	2	3	4	5
16.	When pain comes on strong I think I might become paralyzed or more disabled	0	1	2	3	4	5
17.	I find it hard to concentrate when I hurt	0	1	2	3	4	5
18.	I find it difficult to calm my body down after periods of pain	0	1	2	3	4	5
19.	I worry when I am in pain	0	1	2	3	4	5
20.	I try to avoid activities that cause pain	0	1	2	3	4	5

18.3.6 Center for Epidemiological Studies Depression Scale

Depression Screening

Center for Epidemiologic Studies Depression (CES-D)

Scale Description:
The following scale was developed by the Center for Epidemiologic Studies (Radlof, 1977). The scale has been found reliable (Alpha>.85) in previous research (Hann et. al., 1999). A Spanish version of this scale is also available.

Scale items:
Below is a list of some ways you may have felt or behaved. Please indicate how often you have felt this way during the last week by checking the appropriate space. Please only provide one answer to each question.

	During the past week:	***Rarely*** or none of the time (less than 1 day)	***Some*** or a *little* of the time (1-2 days)	***Occasionally*** or a moderate amount of time (3-4 days)	***Most*** or all of the time (5-7 days)
1.	I was bothered by things that usually don't bother me.				
2.	I did not feel like eating; my appetite was poor.				
3.	I felt that I could not shake off the blues even with help from my family or friends.				
4.	I felt I was just as good as other people.				
5.	I had trouble keeping my mind on what I was doing.				
6.	I felt depressed.				
7.	I felt that everything I did was an effort.				
8.	I felt hopeful about the future.				
9.	I thought my life had been a failure.				
10.	I felt fearful.				
11.	My sleep was restless.				
12.	I was happy.				
13.	I talked less than usual.				
14.	I felt lonely.				
15.	People were unfriendly.				
16.	I enjoyed life.				
17.	I had crying spells.				
18.	I felt sad.				
19.	I felt that people disliked me.				
20.	I could not get going.				

Scoring:	Rarely (Less than 1 day)	Some (1-2 days)	Occasionally (3-4 days)	Most (5-7 days)
Questions 4, 8, 12, and 16	3	2	1	0
All other questions	0	1	2	3

The score is the sum of the 20 questions. Possible range is 0-60. If more than four questions are missing answers, do not score the CES-D questionnaire. A score of 16 points or more is considered depressed.

References:

Hann, D., Winter, K., & Jacobsen, P. (1999) Measurement of depressive symptoms in cancer patients. Evaluation of the Center for Epidemiological Studies Depression Scale (CES-D). Journal of Psychosomatic Research, 46, 437-443.

Radloff, L.S. (1977). The CED-D scale: A self-report depression scale for research in the general population. Applied Psychological Measurement, 1, 385-401.

18.3.7 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]: *specify*: ☐ Allo ☐Hyper _____

YES NO Temperature asymmetry[3] *If yes, specify*: ☐ Cold ☐ Warm ☐ Labile _____

YES NO Color asymmetry[4] *If yes, specify*: ☐ Red ☐ Blue ☐ Other _____

YES NO Sweating asymmetry[5] _____

YES NO Edema[6] _____

YES NO Dystrophic changes[7] *If yes, specify*: ☐ Nails ☐ Hair ☐ Skin _____

YES NO Motor abnormalities[8] *If yes, specify*: ☐ Weak ☐Tremor ☐ Dystonia _____

☐ Decreased ROM ☐ 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] *If yes, specify to*: ☐ Light Touch ☐ Deep Joint Pressure ☐ Vibration ☐ Cold ☐ Heat

YES NO Temperature asymmetry by palpation[11] *If yes, specify*: ☐ Affected Side **Cooler** ☐ Affected Side **Warmer**

YES NO Color asymmetry[12] *If yes, specify*: Affected side: ☐ Red ☐ Blue or Pale ☐ Mottled ☐ Scar

YES NO Asymmetric Edema[13] Notes: _____

YES NO Sweating asymmetry[14] *If yes, specify*: ☐ **Increased** on Affected Side ☐ **Decreased** on Affected Side

YES NO Dystrophic changes[15] *If yes, specify*: ☐ Nails ☐ Hair ☐ Skin. Notes: _____

YES NO Motor abnormalities[16] *If yes, specify*: ☐ Tremor ☐ Dystonia ☐ Decreased Active ROM

☐ Weakness ____/5 (Rate 0-5 of most affected joint)

Version Date: 3/29/2011 CRPS Severity Score

18.5 Health Economics Outcome Questionnaire (sample)

GRÜNENTHAL	**Health Economics Outcome Questionnaire** **Booklet KF7013-03**	Page 1

Subject No. ⌊_⌊_⌊_⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌋

Visit 2 (Day 1) / Visit 9 (Week 26) / Visit 11 (Week 52)

Date of assessment ⌊_⌊_⌋/⌊_⌊_⌊_⌋/⌊_⌊_⌊_⌊_⌋
DD MMM YYYY

HEALTHCARE UTILIZATION

Hospitalization

1. During the past 26 weeks, were you admitted overnight to a hospital (for more than 24 hours)?

☐ Yes ☐ No [SKIP to 2] ☐ Don't know

1.a. If Yes, how many times were you hospitalized in the past 26 weeks? _____(#)

1.b. For each hospitalization (during the past 26 weeks), please provide the diagnosis or reason for hospitalization, number of nights, and admission date:

#	Major Diagnosis or Reason for Hospitalization	# of Nights	Admission Date
1			⌊_⌊_⌋/⌊_⌊_⌊_⌋/⌊_⌊_⌊_⌊_⌋ *DD MMM YYYY*
2			⌊_⌊_⌋/⌊_⌊_⌊_⌋/⌊_⌊_⌊_⌊_⌋ *DD MMM YYYY*
3			⌊_⌊_⌋/⌊_⌊_⌊_⌋/⌊_⌊_⌊_⌊_⌋ *DD MMM YYYY*
4			⌊_⌊_⌋/⌊_⌊_⌊_⌋/⌊_⌊_⌊_⌊_⌋ *DD MMM YYYY*
5			⌊_⌊_⌋/⌊_⌊_⌊_⌋/⌊_⌊_⌊_⌊_⌋ *DD MMM YYYY*
6			⌊_⌊_⌋/⌊_⌊_⌊_⌋/⌊_⌊_⌊_⌊_⌋ *DD MMM YYYY*
7			⌊_⌊_⌋/⌊_⌊_⌊_⌋/⌊_⌊_⌊_⌊_⌋ *DD MMM YYYY*

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.

GRÜNENTHAL	**Health Economics Outcome Questionnaire** **Booklet KF7013-03**	Page 2

Subject No. ⌊_⌊_⌊_⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌋

Emergency Room (ER) Visit

2. During the <u>past 26 weeks</u>, did you receive care in an emergency room <u>without</u> being admitted to the hospital?

☐ Yes ☐ No [SKIP to 3] ☐ Don't know

2.a. If Yes, how many times in the past 26 weeks? _____(#)

2.b. Please list the reason and date for each emergency room visit:

#	Major Reason for ER Visit	Date
1		⌊_⌊_⌋/⌊_⌊_⌊_⌋/⌊_⌊_⌊_⌊_⌋ *DD MMM YYYY*
2		⌊_⌊_⌋/⌊_⌊_⌊_⌋/⌊_⌊_⌊_⌊_⌋ *DD MMM YYYY*
3		⌊_⌊_⌋/⌊_⌊_⌊_⌋/⌊_⌊_⌊_⌊_⌋ *DD MMM YYYY*

Nursing Home (NH) Stay

3. During the past 26 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 26 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			⌊_⌊_⌋/⌊_⌊_⌊_⌋/⌊_⌊_⌊_⌊_⌋ *DD MMM YYYY*
2			⌊_⌊_⌋/⌊_⌊_⌊_⌋/⌊_⌊_⌊_⌊_⌋ *DD MMM YYYY*
3			⌊_⌊_⌋/⌊_⌊_⌊_⌋/⌊_⌊_⌊_⌊_⌋ *DD MMM YYYY*

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.

GRÜNENTHAL	**Health Economics Outcome Questionnaire** **Booklet KF7013-03**	Page 3

Subject No. |_|_|_|_|_| |_|_|_|_|

Outpatient Health Care Provider Contact

4. Which of the following types of health providers have you seen or had a telephone call with in the past 26 weeks on an outpatient basis? Indicate the provider frequency, major diagnosis or reason for visit, and whether care was provided for CRPS-related pain or its symptoms. Please be careful not to double-count services.

#	Provider Type	Used?	# visits in past 26 weeks	# phone calls in past 26 weeks	Major Diagnosis or Reason for Visit/Call
a	Family Medicine, Internist, Primary Care provider	☐ Yes ☐ No ☐ Don't know			
b	Pain specialist	☐ Yes ☐ No ☐ Don't know			
c	Psychiatrist	☐ Yes ☐ No ☐ Don't know			
d	Psychologist	☐ Yes ☐ No ☐ Don't know			
e	Neurologist	☐ Yes ☐ No ☐ Don't know			
f	Physician Assistant / Nurse Practitioner	☐ Yes ☐ No ☐ Don't know			
g	Dentist	☐ Yes ☐ No ☐ Don't know			
h	Podiatrist	☐ Yes ☐ No ☐ 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.

GRÜNENTHAL	Health Economics Outcome Questionnaire Booklet KF7013-03	Page 4

Subject No. |_|_|_|_|_| |_|_|_|_|

#	Provider Type	Used?	# visits in past 26 weeks	# phone calls in past 26 weeks	Major Diagnosis or Reason for Visit/Call
i	Integrated medicine	☐ Yes ☐ No ☐ Don't know			
j	Chiropractor	☐ Yes ☐ No ☐ Don't know			
k	Physical therapist	☐ Yes ☐ No ☐ Don't know			
l	Occupational therapist	☐ Yes ☐ No ☐ Don't know			
m	Visiting nurse	☐ Yes ☐ No ☐ Don't know			
n	Home health aide	☐ Yes ☐ No ☐ Don't know			
o	Other specialty (specify): _____	☐ Yes ☐ No ☐ Don't know			
p	Other specialty (specify): _____	☐ Yes ☐ No ☐ Don't know			
q	Other specialty (specify): _____	☐ Yes ☐ No ☐ 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.

GRÜNENTHAL	**Health Economics Outcome Questionnaire** **Booklet KF7013-03**	Page 5

Subject No. |_|_|_|_|_| |_|_|_|_|

HOME SERVICES, HOME HELP, FORMAL AND INFORMAL CAREGIVING, DEVICES

Home Services and Help

1. Which of the following types of services or help have you used in the past 26 weeks due to your CRPS-related pain?

#	Program/Service Type	Used?	# times in past 26 weeks	Average duration per time (min)
a	Cleaning or homemaking services	☐ Yes ☐ No ☐ Don't know		
b	Meals delivered	☐ Yes ☐ No ☐ Don't know		
c	Formal childcare / babysitting assistance	☐ Yes ☐ No ☐ Don't know		
d	Transportation to help complete daily errands (e.g., shopping, bank, work, medical visits, pharmacy)	☐ Yes ☐ No ☐ Don't know		
e	Formal and informal caregiving	☐ Yes ☐ No ☐ Don't know		

Special Product / Device / Tool

2. Did you use any special equipment/assistive tools the past 26 weeks due to your CRPS-related pain?

Special product / device / tool	Used?	#	Name of device/product/tool
f. Special equipment /assistive tools	☐ Yes ☐ No ☐ 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.

19 PROTOCOL AMENDMENTS

19.1 Protocol amendment 01

Amendment rationale

This amendment is implemented to:

- Remove the requirement for blood sampling for a population pharmacokinetic analysis. A population pharmacokinetic analyses of the cumulative dose of 400 mg is not required because sufficient data have been collected in the trial KF7013-01.
- To follow-up all subjects for up to 52 weeks.
- To add continuous real-time ECG monitoring covering the period of infusions.
- To modify the allowance of medications known to prolong the QT interval.

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:**
Title page	
Trial sites: Multi-site trial (approximately 70 sites in the United States~~, Canada,~~ and European Union)	Trial sites: Multi-site trial (approximately 70 sites in the United States and European Union)
Section 1.1.2: Brief description of the sequence and duration of all trial periods	
Other data to be collected that is not directly attributed to an endpoint	Other data to be collected that is not directly attributed to *or considered as* an endpoint
Section 1.1.1: Flow diagram summary of the trial	
~~The first 100 subjects will be followed through Week 52; subsequent subjects will be followed through Week 26~~	[Deleted]
Section 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, a treatment period consisting of 4 infusions over 10 days, and a follow-up period of approximately 50 weeks (Visit 6 [Week 2] through Visit 11 [Week 52]). ~~After the first 100 subjects have been allocated to treatment, remaining subjects will have a shortened follow-up period of approximately 24 weeks (Visit 6 through Visit 9 [Week 26]).~~ The ~~first 100~~ subjects are expected to be in the trial for approximately 60 weeks (14 months). ~~The remaining subjects are expected to be in the trial for approximately 32 weeks (8 months).~~ See Section 1.1.1 for a summary of the trial as a flow diagram and Section ~~1.7~~ for a tabular schedule of events.	There will be an enrollment period lasting up to 60 days, a treatment period consisting of 4 infusions over 10 days, and a follow-up period of approximately 50 weeks (Visit 6 [Week 2] through Visit 11 [Week 52]). The subjects are expected to be in the trial for approximately 60 weeks (14 months). See Section 1.1.1 for a summary of the trial as a flow diagram and Section *1.6* for a tabular schedule of events.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1.2: Trial objectives, endpoints, and outcomes	
~~To assess the pharmacokinetics of neridronic acid in subjects with CRPS~~ ~~Volume of distribution and clearance of neridronic acid in plasma, based on population pharmacokinetics modeling.~~	[Deleted]
Section 1.3.2: Exclusion criteria	
1. Evidence of renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine equation [Levey et al. 2009] or a urinary albumin creatinine ratio >30 mg/g), based on central safety laboratory data, or a history of chronic kidney disease. ... 3. Vitamin D deficiency, defined as a 25(OH)D level <30 ng/mL, based on central safety laboratory data obtained prior to Visit 2~~.~~ Subjects with vitamin D deficiency should receive appropriate supplementation during the enrollment period. A normal vitamin D level (≥30 ng/mL) must be documented prior to allocation to investigational medicinal product (IMP). ... [New exclusion criteria] ...	1. Evidence of renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine equation [Levey et al. 2009] or a urinary albumin creatinine ratio >30 mg/g), based on central safety laboratory data, or a history of chronic kidney disease. *Note: If 2 consecutive laboratory tests indicate eGFR levels ≥60 mL/min/1.73 m^2 or a single repeat laboratory test of the urinary albumin creatinine ratio is <30 mg/g during the enrollment period, the subject is eligible.* ... 3. Vitamin D deficiency, defined as a 25(OH)D level <30 ng/mL, based on central safety laboratory data obtained prior to Visit 2 *(a single repeat laboratory test is allowed).* Subjects with vitamin D deficiency should receive appropriate supplementation during the enrollment period. A normal vitamin D level (≥30 ng/mL) must be documented prior to allocation to investigational medicinal product (IMP). ... *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, escotalopram) or tricyclic antidepressants 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 until at least 4 days after the last infusion of IMP.* ...

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1.4.3: Prior/concomitant medications or therapies	
The following medications and therapies are forbidden for the duration of the trial: ... • High-dose opioid analgesics (>200 mg morphine equivalent daily dose) or combinations of opioids and benzodiazepines, as these regimens may have potential for significant opioid/sedatives side-effects that may be considered unstable or unsafe. ~~• Drugs with known risk of torsades de pointes.~~ • Nerve blocks, radiofrequency ablation or other sympathectomy procedures, hyperbaric oxygen treatments, ketamine infusions, intravenous immunoglobulin, or other experimental therapies. • Investigational drugs.	The following medications and therapies are forbidden for the duration of the trial: ... • High-dose opioid analgesics (>200 mg morphine equivalent daily dose) or combinations of opioids and benzodiazepines, as these regimens may have potential for significant opioid/sedatives side-effects that may be considered unstable or unsafe. • Nerve blocks, radiofrequency ablation or other sympathectomy procedures, hyperbaric oxygen treatments, ketamine infusions, intravenous immunoglobulin, or other experimental therapies. • Investigational drugs. *The following medications and therapies are forbidden from 7 days prior to allocation until 4 days after the last infusion:* *• Drugs with a known risk of torsades de pointes, excluding selective serotonin re-uptake inhibitor antidepressants (e.g., citalopram, escitalopram) and tricyclic antidepressants if QT interval values met entry criteria, subjects were on a stable dose for at least 1 month prior to enrollment, and doses are expected to stay stable throughout the trial.*
Section 1.5.2: Subject populations	
~~**Pharmacokinetic Set:**~~ ~~All subjects with at least 1 evaluable pharmacokinetic concentration.~~	[Deleted]
Section 1.5.3: Statistical methods and analysis	
Subject disposition will be summarized descriptively for all enrolled subjects. Discontinuations will be summarized descriptively for all allocated subjects. Demographic data, baseline characteristics, medical history, concomitant medications, and exposure will be summarized descriptively for the Safety Set. ~~Pharmacokinetic and~~ Pharmacodynamic parameters will be summarized descriptively for the ~~Pharmacokinetic~~ Set ~~and the Pharmacodynamic Set, respectively~~.	Subject disposition will be summarized descriptively for all enrolled subjects. Discontinuations will be summarized descriptively for all allocated subjects. Demographic data, baseline characteristics, medical history, concomitant medications, and exposure will be summarized descriptively for the Safety Set. Pharmacodynamic parameters will be summarized descriptively for the *Pharmacodynamic* Set.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1.5.3: Statistical methods and analysis: Secondary safety endpoints and other safety data **Section 14.1.6.1: Adverse events**	
The incidences and incidence rates of all adverse events will be summarized descriptively. The distribution of time to onset of any TEAE will be summarized using time-to event methods. A graphical display using Kaplan-Meier methods displaying subjects at risk per time point will also be produced.	The incidences and incidence rates of all adverse events will be summarized descriptively. *Permanent discontinuations from treatment due to adverse events will be summarized descriptively.* The distribution of time to onset of any TEAE will be summarized using time-to event methods. A graphical display using Kaplan-Meier methods displaying subjects at risk per time point will also be produced.
Section 1.6: Pharmacometric analyses	
~~A previously developed population pharmacokinetics model will be updated using the plasma concentration data collected in this trial.~~ ~~Exploratory evaluations of potential exposure-response relationships between neridronic acid exposure levels and selected safety markers (i.e., serum creatinine, eGFR, urinary albumin creatinine ratio, and QT interval assessments) as well as efficacy outcomes and pharmacodynamics markers (bone turnover markers, imaging markers) will be performed, if deemed appropriate.~~ ~~Population pharmacokinetics and pharmacokinetics-pharmacodynamics modeling will be performed by means of a nonlinear mixed effect modeling approach as implemented in NONMEM® Version 7. Other approaches will be applied, if deemed necessary.~~	[Section deleted]
Section 1.6: Schedule of events	
	[Added to Day 1, Day 4, Day 7 and Day 10] *Perform continuous real-time ECG monitoring*
~~Take blood for pharmacokinetic evaluation~~[q]	[Deleted row]
Section 1.6: Schedule of events: Footnotes	
~~e) This will be the final visit for all subjects allocated to treatment after the first 100 subjects allocated.~~	[Deleted]
o) The diagnosis of CRPS must be confirmed according to the clinical diagnostic criteria recommended by the IASP (Budapest clinical criteria). The number of signs and symptoms of CRPS at ~~each visit~~ will be summed for determination of the CRPS Severity Score.	o) The diagnosis of CRPS must be confirmed *using the tablet computer at Visit 1* according to the clinical diagnostic criteria recommended by the IASP (Budapest clinical criteria) *(Section 12.2.3.1)*. The number of signs and symptoms of CRPS at *Visit 2, and Visit 7 to Visit 11, inclusive,* will be summed for determination of the CRPS Severity Score *(Section 12.4.8)*.
~~q) For Visit 2 through Visit 5, 1 blood sample for pharmacokinetic evaluation should be taken between~~	[Deleted]

Changes to this protocol include:	
Formerly read:	**Now reads:**
~~5 minutes and 10 minutes prior to the start of the infusion and 1 blood sample from 45 minutes to 5 minutes prior to the end of the infusion.~~ ~~For Visit 2 and Visit 5, an additional sample should be taken between 5 minutes and 60 minutes after the end of the infusion.~~ ~~For Visit 6, a single blood sample should be taken during the visit following all non-invasive procedures.~~ ~~Blood samples for pharmacokinetic evaluation should be taken from a limb different to that used for the infusion and must not be taken from the infusion line.~~	
...	...
s) For women of child-bearing potential, a negative urine pregnancy test result must be obtained prior to each infusion. ~~Pregnancy testing should also be performed at Visit 11 for the first 100 subjects allocated or at Visit 9 for subjects allocated to treatment after the first 100 subjects have been allocated~~. For subjects who discontinue the trial prior to completion, pregnancy testing should be performed at the Early Termination Visit (whose procedures are identical to Visit 11).	s) For women of child-bearing potential, a negative urine pregnancy test result must be obtained prior to each infusion. For subjects who discontinue the trial prior to completion, pregnancy testing should be performed at the Early Termination Visit (whose procedures are identical to Visit 11).
t) The subject card is to be returned at the final visit or at the Early Termination Visit in the case of early discontinuation from the trial. ~~After the first 100 subjects are allocated, the final visit for all subsequent subjects will be Visit 9 (Week 26).~~	t) The subject card is to be returned at the final visit or at the Early Termination Visit in the case of early discontinuation from the trial.
Section 8.1: Discussion of the trial design	
...	...
Normal bone mineralization and bone formation were observed in biopsies from regions of non-pagetic bone (iliac crest), and improved indices of bone turnover were observed in regions of pagetic bone. It is anticipated that 15 evaluable biopsy specimens will be adequate to confirm normal bone mineralization in the iliac crest at approximately 6 months following treatment with neridronic acid 400 mg. Biopsies will be obtained from approximately 20 subjects to obtain 15 evaluable biopsy specimens. ~~Biopsies will be obtained from approximately 20 subjects to obtain 15 evaluable biopsy specimens.~~	Normal bone mineralization and bone formation were observed in biopsies from regions of non-pagetic bone (iliac crest), and improved indices of bone turnover were observed in regions of pagetic bone. *Biopsies will be obtained from approximately 20 subjects to obtain 15 evaluable biopsy specimens.* It is anticipated that 15 evaluable biopsy specimens will be adequate to confirm normal bone mineralization in the iliac crest at approximately 6 months following treatment with neridronic acid 400 mg. Biopsies will be obtained from approximately 20 subjects to obtain 15 evaluable biopsy specimens. *A 6 month time point was selected for the biopsy in order to match the slow kinetics of bone matrix and mineral apposition in humans, with approximately 6 months required to complete a single remodeling cycle (Riggs and Parfitt 2005).*

Changes to this protocol include:

<table>
<tr><th>Formerly read:</th><th>Now reads:</th></tr>
<tr><td colspan="2">Section 8.2: Benefit/risk analysis: Risks related to bone biopsies</td></tr>
<tr><td>Bone biopsies are performed as a minor outpatient surgery and are safe and generally well-tolerated (Kann et al. 2006, Hernandez et al. 2008). Risks include bleeding, hematoma, infection, superficial nerve injury, and pain. Most subjects experience soreness over the biopsy area for 4 days to 5 days. Subjects with increased risk of bleeding (e.g., hemostasis disorders, concomitant treatment with antithrombotic drugs) will be excluded from the bone biopsy assessments.</td><td>Bone biopsies are performed as a minor outpatient surgery and are safe and generally well-tolerated (Kann et al. 2006, Hernandez et al. 2008). Risks include bleeding, hematoma, infection, superficial nerve injury, and pain. Most subjects experience soreness over the biopsy area for 4 days to 5 days. Subjects with increased risk of bleeding (e.g., hemostasis disorders, concomitant treatment with antithrombotic drugs) will be excluded from the bone biopsy assessments.
It is unknown whether a bone biopsy could trigger or worsen CRPS in patients. The limited trials in which bone biopsies were performed in patients with CRPS or similar painful conditions have not suggested that this procedure would be likely to cause severe complications or worsening of CRPS, even when performed in a CRPS-affected region. Since biopsies will be performed only in a region free of CRPS-related signs and symptoms, this is likely to mitigate the risk of worsening of the condition.</td></tr>
<tr><td colspan="2">Section 9.3.1: Subject discontinuation from the trial</td></tr>
<tr><td>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
<table>
<tr><th></th><th colspan="2">Discontinuation from trial</th></tr>
<tr><th>Reason</th><th>Compulsory</th><th>Optional</th></tr>
<tr><td>Enrollment failure (i.e., subject was not allocated to treatment due to failure to meet inclusion</td><td>X</td><td></td></tr>
</table></td><td>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
<table>
<tr><th></th><th colspan="2">Discontinuation from trial</th></tr>
<tr><th>Reason</th><th>Compulsory</th><th>Optional</th></tr>
<tr><td>Enrollment failure (i.e., subject was not allocated to treatment due to failure to meet inclusion or exclusion criteria and</td><td>X</td><td></td></tr>
</table></td></tr>
</table>

Changes to this protocol include:

Formerly read:			**Now reads:**		
or exclusion criteria and did not receive IMP)			did not receive IMP*)*.		
Subject withdrawal of consent (the reason for withdrawal must be specified~~)~~	X		**Subject withdrawal of consent** (the reason for withdrawal must be specified*)*.	X	
Subject death	X		**Subject death.**	X	
Subject loss to follow-up (i.e., no further contact with the subject is possible)	X		**Subject loss to follow-up** (i.e., no further contact with the subject is possible*)*.	X	
Sponsor decision to discontinue the subject	X		**Sponsor decision to discontinue the subject.**	X	
~~**Adverse event** (e.g., subject experiences a significant deterioration in health such that further participation in the trial may jeopardize their ability to obtain other treatment)~~		~~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
~~**Major protocol deviation** (e.g., serious non-compliance with protocol procedures, unsafe use of forbidden medications, 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~~	**Sponsor decision to terminate the trial.**	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	**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
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		X			

Changes to this protocol include:

Formerly read:	**Now reads:**
objective participation in the trial)	
Section 9.3.2: Subject discontinuation from the IMP	
Discontinuation of IMP applies only to the treatment period. Subjects who are discontinued from IMP should be encouraged to remain in the trial ~~for follow-up assessments~~ for their own safety and for the integrity of the trial. The investigator may decide to temporarily ~~suspend~~ a subject from ~~the IMP at any point during the treatment period~~ if further ~~assessment~~ may be helpful to assure safety of the subject. ~~In situations where treatment is temporarily discontinued (e.g., due to a potential safety concern or scheduling issue), and a decision is made (in consultation with the sponsor or sponsor's designee) to resume treatment, the treatment period can be extended up to 21 days (i.e., Visit 5 should occur no later than 21 days after Visit 2). A minimum period of 48 hours is required between infusions.~~ ~~Investigators~~ may 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 ~~evidence of dehydration or~~ deterioration in the subject's health for reasons related or unrelated to the treatment. ~~A subject must be discontinued from treatment if any of the following events occur during the treatment period:~~ ~~• Symptomatic hypocalcemia.~~ ~~• A persistent change in renal function, based on the following criteria:~~ ~~– A 25% decrease from baseline in eGFR, relative to the last value obtained prior to treatment, observed on repeated serum creatinine measurements from the central safety laboratory at least one week apart. Subjects with any single 25% decrease in eGFR must be temporarily suspended from treatment and reassessed; if the repeated measurement of eGFR is within 80% or more of the baseline value, the subject may resume treatment.~~ ~~– Evidence of albuminuria based on a quantitative (central safety laboratory) urinary albumin creatinine ratio of >300 mg/g. The subject may resume treatment if the finding is confirmed to be <30 mg/g based on 2 consecutive urine~~	Discontinuation of IMP applies only to the treatment period. Subjects who are discontinued from IMP should *not be discontinued from the trial except for the 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* 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, the treatment period may be extended to a maximum of 21 days (i.e., Visit 5 should occur no later than 21 days after Visit 2). Visit 6 will be scheduled to occur 4 days (±2 days) after Visit 5, but all subsequent visits should occur as originally scheduled relative to Visit 2 (e.g., Visit 7 will be 42 days [6 weeks] after Visit 2). No more than 4 infusions may be administered during the treatment period, and a minimum of 48 hours between any 2 infusions is required.* *Table 2: Reasons for permanent and temporary discontinuation of subjects from IMP* ***Discontinuation from IMP*** ***Reason*** / ***Permanent*** / ***Temporary*** *Symptomatic hypocalcemia.* / *X* *Serum calcium* / / *X*

Changes to this protocol include:		
Formerly read:	**Now reads:**	
~~samples, more than 1 day apart, analyzed at the central safety laboratory.~~ ~~– An eGFR <50 mL/min/1.73m^2 and urinary albumin creatinine ratio >150 mg/g.~~ ~~• An average QTcF interval of >500 ms, or average QTcF interval of >480 ms with a concurrent increase in average QTcF interval >60 ms from enrollment (average of 3 ECGs).~~ ~~• Pregnancy.~~ ~~• Development of hypersensitivity to the IMP.~~ ~~Central safety laboratory data from the previous visit, in particular eGFR, must be evaluated prior to each infusion.~~ 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 ~~3~~ days may resume treatment. Subjects with persistent signs and symptoms of ocular inflammation must be discontinued from IMP and undergo an ophthalmologic examination.	*<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.* *Clinical signs of dehydration (e.g., dizziness, palpitations, confusion).* *Evidence suggestive of a possible change in renal function:* *• A persistent ≥25% decrease from baseline (last value observed prior to treatment) in the eGFR, based on repeated central laboratory results from blood samples obtained at least 1 week apart*[a]. *• A ≥25% decrease from baseline in the eGFR. If a repeated measurement of eGFR is within 75% or more of the baseline value, the subject may resume treatment*[a]. *• A persistent urinary ACR >300 mg/g based on quantitative urinary albumin and creatinine data from the central laboratory, with urine samples obtained at least 1 week apart.* *• 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*	*X* *X* *X* *X*

Changes to this protocol include:			
Formerly read:	**Now reads:**		
	creatinine data from the central laboratory indicate a urinary ACR value <30 mg/g.		
	• A persistent eGFR <50 mL/min/1.73m^2 and urinary ACR >150 mg/g based on repeated quantitative data from the central laboratory, with blood and urine samples obtained at least 1 week apart.	*X*	
	• An eGFR <50 mL/min/1.73m^2 and urinary ACR >150 mg/g based on results of the central laboratory or semiquantitative urinary dipstick.		*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]		
	• Resolution of signs and symptoms within 5 days.		*X*
	• Persistent signs and symptoms.	*X*	
	At any point during the treatment period if further assessment may be helpful to assure safety of the subject.		*X*

Changes to this protocol include:	
Formerly read:	**Now reads:**
	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 prohibited 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) Baseline values of eGFR are obtained from central laboratory results after Visit 2 (based on the blood sample taken at Visit 2 prior to the first administration of IMP). Evaluation of change from baseline in eGFR must occur prior to Visit 4 and Visit 5, based on assessment of central laboratory results from blood samples taken prior to Visit 3 and Visit 4, respectively.* *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 signs and symptoms of ocular inflammation must be discontinued from IMP and undergo an ophthalmologic examination.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 10.1.2: Preparation	
The volume of IMP transferred to the infusion bag must be recorded ~~and the transfer procedure must be witnessed by a second individual who documents confirmation of the transferred volume~~.	The volume of IMP transferred to the infusion bag must be recorded.
Section 10.2: Administration of investigational medicinal product	
The full contents of a single ampule or 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 neridronic acid 400 mg. The complete solution volume of 500 mL should be administered at each infusion visit unless treatment is suspended for safety reasons.	The full contents of a single ampule or 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 neridronic acid 400 mg. The complete solution volume of 500 ± *50* mL should be administered at each infusion visit unless treatment is suspended for safety reasons.
Section 11.1: Course of the trial	
All visits should be attended in a fasting state (at least 8 hours).	All visits should be attended in a fasting state (at least 8 hours). *A non-fasting state does not constitute a protocol deviation.*
Section 11.1.1.1: Visit 1 (Day -60 to Day -1)	
• ~~Complete the assessment of the signs and symptoms~~ of CRPS (for further details, see Section 12.2.3.1).	• *The diagnosis of* CRPS *must be confirmed using the tablet computer at Visit 1 according to the clinical diagnostic criteria recommended by the IASP (Budapest clinical criteria)* (for further details, see Section 12.2.3.1).
Section 11.1.2.1: Visit 2 (Day 1) **Section 11.1.2.2: Visit 3 (Day 4; ±1 day)** **Section 11.1.2.3: Visit 4 (Day 7; ±1 day)** **Section 11.1.2.4: Visit 5 (Day 10; ±1 day)**	
Record triplicate 12-lead ECG (once at least 15 minutes before the infusion and once at least 15 minutes after the infusion). Record concomitant medications and therapies. ... Collect urine for central safety laboratory urinalysis and local dipstick evaluation (calculate urinary albumin creatinine ratio). ~~Take blood for pharmacokinetic evaluation (before, during, and after infusion; see Section 1.7 for time points).~~	Record triplicate 12-lead ECG (once at least 15 minutes before the infusion and once at least 15 minutes after the infusion). *Perform continuous real-time ECG monitoring (for details, see Section 12.3.4).* Record concomitant medications and therapies. ... Collect urine for central safety laboratory urinalysis and local dipstick evaluation (calculate urinary albumin creatinine ratio).

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 11.1.3.1: Visit 6 (Week 2; ±2 days)	
Collect urine for central safety laboratory urinalysis. ~~Take blood for pharmacokinetic evaluation (see Section 1.7 for time point).~~	Collect urine for central safety laboratory urinalysis.
Section 11.1.3.4: Visit 9 (Week 26; ±15 days)	
A single bone biopsy will be obtained from the iliac crest, following tetracycline double-labeling, in a subset of subjects (from US sites only). The biopsy should be scheduled to be performed 26 weeks after the first administration of IMP. Biopsies will be obtained from approximately 20 subjects to obtain 15 evaluable biopsy specimens. ~~This will be the final visit for all subjects allocated to treatment after the first 100 subjects allocated.~~	A single bone biopsy will be obtained from the iliac crest, following tetracycline double-labeling, in a subset of subjects (from US sites only). The biopsy should be scheduled to be performed 26 weeks after the first administration of IMP. Biopsies will be obtained from approximately 20 subjects to obtain 15 evaluable biopsy specimens.
Section 11.2: Examination hierarchy and time windows	
Electrocardiograms 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.	Electrocardiograms should be taken before invasive procedures. When practical, blood samples for safety laboratory evaluation should be taken after all non-invasive procedures (including completion of questionnaires) have been finished.
Section 12.1: Overview of blood sampling in this trial	
The total blood volume drawn per subject will be approximately ~~250~~ mL during the trial (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).	The total blood volume drawn per subject will be approximately *200* mL during the trial (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).
Section 12.1: Overview of blood sampling in this trial: Table 2	
~~Pharmacokinetic evaluation [a] 4 mL 11 44 mL~~ Total (US sites) ~~51~~ ~~217~~.5 mL Total (EU sites) ~~62~~ ~~245~~ mL	[Row deleted] Total (US sites) *40* *173*.5 mL Total (EU sites) *51* *201* mL
Section 12.1: Overview of blood sampling in this trial: Table 2: Footnotes	
~~a) Population pharmacokinetics will be analyzed on an ongoing basis throughout the trial.~~ ~~b~~) Includes vitamin D testing.	*a*) Includes vitamin D testing.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 12.2.3.1: Diagnosis of CRPS	
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.	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 active range of motion, or weakness) (see Section 18.4).*
Section 12.3.4: Continuous real-time ECG monitoring	
[New Section]	*Continuous real-time ECG monitoring, which may be performed by telemetry, will be performed at the infusion visits (Day 1, Day 4, Day 7, and Day 10), starting at least 30 minutes prior to the beginning of each infusion and for up to at least 30 minutes after the end of each infusion. Continuous real-time ECG monitoring must be performed by a qualified person. Personnel trained in advanced cardiopulmonary resuscitation must be on site and readily available to treat any potential cardiac rhythm disturbances.* *Electrocardiogram machines may be used for continuous real-time ECG monitoring.*
Section 12.3.5: Safety laboratory: Hematology panel	
White blood cell (WBC) count with differential count ~~if abnormal~~	White blood cell (WBC) count with differential count

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 12.3.8: Bone biopsy procedures	
An iliac crest biopsy will be obtained 5 days to 14 days after the last dose of tetracycline according to procedures of Dempster and Shane (1995). Biopsies will be performed using a Bordier type biopsy needle with a minimum internal diameter of 7.5 mm to ensure an adequate sample size. Evaluable biopsies must contain inner and outer cortical plates with intervening cancellous bone. The biopsy will be performed only by investigators who are skilled and experienced in this procedure. For subjects with lower limb CRPS, the biopsy must be taken from the hip contralateral to the CRPS-affected limb.	An iliac crest biopsy will be obtained 5 days to 14 days after the last dose of tetracycline according to procedures of Dempster and Shane (1995). *Prior to the bone biopsy, subjects may receive optional intravenous sedation. The site of the biopsy will be numbed with a local anesthetic (e.g., xylocaine, lidocaine) to minimize discomfort.* Biopsies will be performed using a Bordier type biopsy needle with a minimum internal diameter of 7.5 mm to ensure an adequate sample size. Evaluable biopsies must contain inner and outer cortical plates with intervening cancellous bone. The biopsy will be performed only by investigators who are skilled and experienced in this procedure. For subjects with lower limb CRPS, the biopsy must be taken from the hip contralateral to the CRPS-affected limb. *Subjects will return to the bone biopsy center 7 days to 10 days after the bone biopsy to have stitches removed.*
Section 12.2.4.2: Urine drugs of abuse test	
Subjects who are receiving benzodiazepines ~~for medical purposes~~ or opioids ~~or opioid-containing medications~~ may participate even if the test ~~for benzodiazepine or opioids~~ is positive.	Subjects who are receiving *stable doses of prescribed medications containing amphetamines,* benzodiazepines*,* or opioids may participate even if the test is positive.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 12.5: Collection of plasma concentration data	
~~Blood sampling for bioanalysis~~ ~~Details of the blood sample collection times are given in the schedule of events (Section 1.7).~~ ~~The exact sampling time must be recorded in the CRF.~~ ~~The blood samples 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 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 for further bioanalytical analysis if deemed necessary.~~ ~~The bioanalytical report (PK1729A), including a description of the assay and a summary of the assay performance data, will be included in the final integrated clinical trial report.~~	[Sections deleted]
Section 14.1.8: Analysis of neridronic acid plasma concentration data	
~~Neridronic acid plasma concentrations at the respective time points will be summarized using descriptive statistics and optionally graphs for the Pharmacokinetic Set.~~	[Section deleted]

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 14.2: Pharmacometric analyses	
~~The population pharmacokinetics and population pharmacokinetics-pharmacodynamics modeling and simulation in this trial will be planned and performed by sponsor personnel or by authorized sponsor delegates.~~ ~~A previously developed population pharmacokinetics model will be updated using the plasma concentration data collected in this trial.~~ ~~Exploratory evaluations of potential exposure-response relationships between neridronic acid exposure levels and selected safety markers (i.e., serum creatinine, eGFR, urinary albumin creatinine ratio, QT interval assessments) as well as efficacy outcomes and pharmacodynamics markers (bone turnover markers, imaging markers) will be performed, if deemed appropriate.~~ ~~Population pharmacokinetics and population pharmacokinetics-pharmacodynamics modeling will be performed by means of a nonlinear mixed effect modeling approach as implemented in NONMEM® Version 7. Other approaches will be applied, if deemed necessary.~~ ~~The results of this analysis will be reported in a pharmacometric report, i.e., separately from the integrated clinical trial report.~~	[Section deleted]
Section 14.1.12: Ad hoc meta-analyses	
Data collected in this trial may be used for ad hoc meta-analyses~~, e.g., to explore pharmacokinetic/pharmacodynamic relationships~~. These meta-analyses will be planned, performed, and reported by sponsor personnel or by authorized sponsor delegates in accordance with sponsor SOPs.	Data collected in this trial may be used for ad hoc meta-analyses. These meta-analyses will be planned, performed, and reported by sponsor personnel or by authorized sponsor delegates in accordance with sponsor SOPs.
Section 16.6: Trial results reporting	
A final report integrating clinical~~, pharmacokinetic~~, pharmacodynamics and statistical results will be prepared by the sponsor. The international coordinating investigator will approve the final report on behalf of the participating investigators.	A final report integrating clinical, pharmacodynamics and statistical results will be prepared by the sponsor. The international coordinating investigator will approve the final report on behalf of the participating investigators.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 17: References: 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. *...* *Jung K, Lein, M. Bone turnover markers in serum and urine as diagnostic, prognostic and monitoring biomarkers of bone metastasis. Biochim Biophys Acta 2014; 1846:425-438.* *...* *Naylor K, Eastell R. Bone turnover markers: use in osteoporosis. Nat Rev Rheumatol 2012; 8(7): 379-89.* *...* *Riggs BL, Parfitt AM. Drugs used to treat osteoporosis: the critical need for a uniform nomenclature based on their action on bone remodeling. J Bone Miner Res 2005; 20 (2): 177-84.*
Section 18.3.7: Work Productivity and Activity Impairment Questionnaire: CRPS	
CPRS had no effect on daily activities	CPRS had no effect on *my* daily activities

19.2 Protocol amendment 02

Amendment rationale

This amendment is implemented to:

- Exclude subjects who are taking forbidden concomitant medications/therapies or are not able to follow the rules for use of concomitant medications/treatments.
- Revise the dose rationale to include additional information from a previous pilot study.
- State that treatment discontinuation will be permanent if eye symptoms reoccur.
- Clarify the distribution of ampules and vials during the trial.

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 1.3.2: Exclusion criteria	
18. Subject is engaged in litigation related to their disability from CRPS in which monetary gain or loss (or	18. Subject is engaged in litigation related to their disability from CRPS in which monetary gain or loss (or

Changes to this protocol include:	
Formerly read:	**Now reads:**
other compensation) may affect their objective participation in the trial.	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 1.4.3).*
Section 1.4.1: Investigational medicinal product	
The first batch of IMP ~~is supplied~~ in glass ampules, each containing 108 mg sodium neridronate hemi hydrate (equivalent to 100 mg neridronic acid) in a total volume of 8 mL. Subsequent batches of IMP will be supplied in vials.	The first batch of IMP *will be provided to sites in the US* in glass ampules, each containing 108 mg sodium neridronate hemi hydrate (equivalent to 100 mg neridronic acid) in a total volume of 8 mL. Subsequent batches of IMP will be supplied in vials. *Sites in the EU will receive all batches of IMP in glass vials.*
Section 8.1.1: Rationale for the investigational medicinal product and the selected dose	
A placebo-controlled trial in 82 subjects with CRPS-I indicated that 400 mg of neridronic acid, administered as four 2-hour infusions of 100 mg in 10 days, is safe, well-tolerated and effective for treatment of pain and other symptoms of CRPS (Varenna et al. 2013).	A placebo-controlled trial in 82 subjects with CRPS-I indicated that 400 mg of neridronic acid, administered as four 2-hour infusions of 100 mg in 10 days, is safe, well-tolerated and effective for treatment of pain and other symptoms of CRPS (Varenna et al. 2013). *A pilot trial of neridronic acid involving cumulative intravenous doses of 200 mg, 300 mg, and 400 mg neridronic acid in patients with CRPS-I suggested that the 400 mg cumulative dose was optimally effective. As the 4 x 100 mg dose regimen 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 neridronic acid 100 mg to treat Paget's disease of bone, osteogenesis imperfecta, and CRPS-I is 2 hours. To limit the maximum concentrations (C_{max}) in this trial to levels similar to those obtained in the KF7013-01 trial, in which neridronic acid 62.5 mg was infused in 2 hours, the infusion time has been extended to 4 hours.* *Alternative dosage forms or routes of administration for neridronic acid are limited to an intramuscular dosage form (25 mg per ampule, available in Italy), which would be impractical for administering a 400 mg total dose. An oral dosage form is not available and would have practical limitations due to the very low bioavailability of bisphosphonates (typically reported in the range of 1%).*
Section 9.3.2: Subject discontinuation from the IMP	
Table 2: Reasons for permanent and temporary discontinuation of subjects from IMP […] • Persistent signs and symptoms~~.~~	Table 2: Reasons for permanent and temporary discontinuation of subjects from IMP […] • Persistent *or recurrent* signs and symptoms

Changes to this protocol include:	
Formerly read:	**Now reads:**
[…] Subjects with resolution of signs and symptoms within 5 days may resume treatment. Subjects with persistent signs and symptoms of ocular inflammation must be discontinued from IMP and undergo an ophthalmologic examination.	[…] 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.
Section 10.1.2: Preparation	
The first batch of IMP will be provided in glass ampules and must be removed using a filter needle (to remove any possible glass particles). Instructions will be provided for proper handling of ampules and filter needles. Subsequent batches of IMP will be supplied in vials, which do not require the use of filter needles. Instructions will be provided for the proper handling of vials.	The first batch of IMP will be provided *to sites in the US* in glass ampules and must be removed using a filter needle (to remove any possible glass particles). Instructions will be provided for proper handling of ampules and filter needles. Subsequent batches of IMP will be supplied in vials, which do not require the use of filter needles. Instructions will be provided for the proper handling of vials. *Sites in the EU will receive all batches of IMP in glass vials.*
Section 10.1.3: Packaging and labelling	
The IMP will be supplied in kits consisting of 4 ampules or 4 vials of IMP.	The IMP will be supplied in kits consisting of *either* 4 ampules *(initially for US sites)* or 4 vials *(US and EU sites)* of IMP.

19.3 Protocol amendment 03

Amendment rationale

This amendment is implemented to:

- Apply all changes introduced in protocol amendment 02 (valid for Germany) to all countries.
- Clarify that Visit 1 does not need to be performed in a fasted state.
- Adjust the duration of stable contraceptive use from 2 months to 1 month prior to allocation.
- Allow repeat testing of eGFR, ACR, serum calcium or magnesium, and vitamin D level.
- Clarify that the combination of opioids and benzodiazepines is forbidden only if the combination is felt to jeopardize subject safety, in the opinion of the investigator.
- Introduce re-enrollment of suitably qualified subjects who failed allocation due to technical reasons.
- Clarify that the drugs of abuse testing is performed at the site and that the investigator should judge whether subjects who are receiving stable doses of prescribed medications containing amphetamines, benzodiazepines, or opioids can participate (together with approval by the sponsor).
- Exclude subjects who are incapable of signing the informed consent.

- Only include subjects who have failed at least 2 available treatments for CRPS, 1 of which must be a pharmacologic treatment.
- Adjust the exclusion criterion for urinary ACR from <30 mg/g to <150 mg/g, due to impact on enrollment of subjects with moderate levels of urinary albumin and based on lack of evidence for changes in urinary ACR in the KF7013-01 trial.
- Adjustment of the temporary IMP discontinuation criteria to allow resumption of treatment if the urinary ACR is <150 mg/g, and removal of the temporary discontinuation criterion for eGFR <50 mL/min/1.73 m^2 and urinary ACR >150 mg/g. A persistent change of this magnitude remains as a criterion for permanent discontinuation.
- Adapt the time period for collection of dental history.
- Clarify that the definition of the pharmacodynamics set includes only subjects who have been treated.
- Clarify requirements for documentation of abnormal laboratory values. Only values that are outside of the sponsor-defined alert ranges require documentation in the CRF. Laboratory values that are outside of the laboratory reference ranges do not require documentation in the CRF.

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 1.3.1: Inclusion criteria	
5. In stable treatment and follow-up therapy for CRPS for at least 1 month prior to allocation to treatment (Visit 2). […] 6. Women of child-bearing potential must have a negative urine beta-human chorionic gonadotropin (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 <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 ~~2 months~~ prior to Visit 2 and for the duration of the trial.	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 trials of at least 2 treatments for CRPS, one of which must be a pharmacologic treatment (see Section 1.4.3).* […] 6. Women of child-bearing potential must have a negative urine beta-human chorionic gonadotropin (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 <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.
Section 1.3.2: Exclusion criteria	
1. Evidence of renal impairment (estimated glomerular	1. Evidence of renal impairment (estimated glomerular

Changes to this protocol include:	
Formerly read:	**Now reads:**
filtration rate [eGFR] <60 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine equation [Levey et al. 2009] or a urinary albumin creatinine ratio ~~>30~~ mg/g), based on central safety laboratory data, or a history of chronic kidney disease. Note: ~~If 2 consecutive laboratory tests indicate eGFR levels ≥60 mL/min/1.73 m^2 or~~ a single repeat laboratory test ~~of the urinary albumin creatinine ratio~~ is ~~<30 mg/g during the enrollment period, the subject is eligible~~. […]	filtration rate [eGFR] <60 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine equation [Levey et al. 2009] or a urinary albumin creatinine ratio [ACR] *>150* mg/g), based on central safety laboratory data *obtained prior to Visit 2*, or a history of chronic kidney disease. Note: a single repeat laboratory test is *allowed*. […]
3. Vitamin D deficiency, defined as a 25(OH)D level <30 ng/mL, based on central safety laboratory data obtained prior to Visit 2 (~~a single~~ repeat laboratory ~~test is~~ allowed). Subjects with vitamin D deficiency should receive appropriate supplementation during the enrollment period. A ~~normal~~ vitamin D level ~~(~~≥30 ng/mL~~)~~ must be documented prior to allocation to investigational medicinal product (IMP). […]	3. Vitamin D deficiency, defined as a 25(OH)D level <30 ng/mL, 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 must be documented prior to allocation to investigational medicinal product (IMP). […]
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~~. […]	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 *2*. […]
19. Subjects taking forbidden concomitant medications/therapies or not being able to follow the rules of use of concomitant treatment (see Section 1.4.3).	19. Subjects taking forbidden concomitant medications/therapies or not being able to follow the rules of use of concomitant treatment (see Section 1.4.3). *20. Subjects incapable of signing the informed consent.*
Section 1.4.3: Prior/concomitant medications or therapies	
Subjects ~~enrolled in the trial~~ are encouraged to continue standard of care… […] The following medications and therapies ~~are forbidden for the duration of~~ the trial: • Drugs with the potential to cause hypocalcemia (e.g., aminoglycosides). Subjects on a stable dose of furosemide or other loop diuretics may ~~continue~~ treatment as long as no dosage changes are anticipated and calcium levels ~~remain~~ in the reference ~~range~~. • Oral or intravenous bisphosphonates, calcitonin, denosumab, or other bone-active drugs (e.g., teriparatide). • High-dose opioid analgesics (>200 mg morphine equivalent daily dose) or combinations of opioids and	*Enrolled subjects must have failed trials of at least 2 treatments for CRPS, 1 of which must be a pharmacologic treatment. A failed trial is defined by continuing pain. Such treatments may be prior to or continuing at enrollment and can include any analgesic medication (including non-steroidal anti-inflammatory drugs [NSAIDs], opioids, antidepressants, etc.), interventional therapy (e.g., nerve block or spinal cord stimulation), or physical therapy.* Subjects are encouraged to continue standard of care… […] The following *are forbidden as concomitant* medications and therapies *during* the trial: • Drugs with the potential to cause hypocalcemia (e.g., aminoglycosides). Subjects on a stable dose of furosemide or other loop diuretics may *receive* treatment

Changes to this protocol include:	
Formerly read:	**Now reads:**
benzodiazepines~~, as these regimens may~~ have potential for significant opioid/sedatives side-effects that may be considered unstable or unsafe~~.~~ […] • Drugs with a known risk of torsades de pointes, excluding selective serotonin re-uptake inhibitor antidepressants (e.g., citalopram, escitalopram) and tricyclic antidepressants if QT interval values met entry criteria, subjects were on a stable dose for at least 1 month prior to ~~enrollment~~, and doses are expected to stay stable throughout the trial.	*with IMP* as long as no dosage changes *in the diuretic medications* are anticipated and calcium levels *are* in the reference *ranges*. • Oral or intravenous bisphosphonates, calcitonin, denosumab, or other bone-active drugs (e.g., teriparatide). • High-dose opioid analgesics (>200 mg morphine equivalent daily dose) or combinations of opioids and benzodiazepines *or any other treatment regimen 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).* […] • Drugs with a known risk of torsades de pointes, excluding selective serotonin re-uptake inhibitor antidepressants (e.g., citalopram, escitalopram) and tricyclic antidepressants if QT interval values met entry criteria, subjects were on a stable dose for at least 1 month prior to *allocation*, and doses are expected to stay stable throughout the trial.
Section 1.5.2: Subject populations	
Pharmacodynamic Set: All subjects with at least 1 non-missing value for at least 1 of the bone turnover markers.	**Pharmacodynamic Set:** All *treated* subjects with at least 1 non-missing value for at least 1 of the bone turnover markers.
Section 1.6: Schedule of events	
~~Collect~~ urine ~~for~~ drugs of abuse testing […] All visits should be attended in a fasting state (at least 8 hours). […] e) Dental history will include: date of last dental visit; dental extractions and other invasive dental surgery in past ~~12~~ months;	*Perform* urine drugs of abuse testing […] All visits*, except Visit 1,* should be attended in a fasting state (at least 8 hours). […] e) Dental history will include: date of last dental visit; dental extractions and other invasive dental surgery in past *3* months *prior to the Enrollment Visit*;
Section 8.2: Benefit/risk analysis	
Hypocalcemia […] 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. All subjects will be provided with supplemental calcium and vitamin D, starting from Visit 1 and continuing through to the end of the trial. Recommended doses are	*Hypocalcemia* […] 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 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

Changes to this protocol include:	
Formerly read:	**Now reads:**
500 mg to 1000 mg per day elemental calcium and approximately 1000 IU/day vitamin D. A combination product of calcium and vitamin D may be used. Subjects with vitamin D ~~deficiency (<~~30 ng/mL~~)~~ at enrollment ~~may~~ receive higher doses of vitamin D during the enrollment period (e.g., 10 000 IU/day for 10 days) to ~~raise vitamin D levels to~~ protocol required levels. Vitamin D will be reduced to approximately 1000 IU/day prior to ~~starting~~ treatment at Visit 2. Investigators should promote compliance by instructing the subject to take the supplements as prescribed and by stating that compliance is important for subject safety. […]	and vitamin D, starting from Visit 1 and continuing through to the end of the trial. Recommended doses are 500 mg to 1000 mg per day elemental calcium and approximately 1000 IU/day vitamin D. A combination product of calcium and vitamin D may be used. Subjects with vitamin D *levels below* 30 ng/mL at enrollment *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. Vitamin D will be reduced to approximately 1000 IU/day prior to *the start of* treatment at Visit 2. *Repeat laboratory testing for vitamin D is permitted during the enrollment period (up to a maximum of 4 times in 60 days).* Investigators should promote compliance by instructing the subject to take the supplements as prescribed and by stating that compliance is important for subject safety. […]
Pregnancy and breastfeeding There ~~is no clinical experience with pregnant or lactating subjects treated with neridronic acid.~~ 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. […]	*Pregnancy and breastfeeding* There *are no adequate and well-controlled trials of neridronic acid in pregnant or lactating women. Although there are no data to suggest a 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. […]
Conclusion As there are currently no Food and Drug Administration (FDA) approved treatments for ~~serious chronic~~ pain ~~conditions~~ with ~~unmet medical needs and there is~~ limited ~~clinical evidence for benefit of available pain medications~~, the potential for benefit of neridronic acid is considered to outweigh the potential risk. The need for controlled safety as well as efficacy trials of potential new treatments for CRPS justifies this trial on moral and ethical grounds.	**Conclusion** As there are currently no Food and Drug Administration (FDA) approved 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 safety as well as efficacy trials of potential new treatments for CRPS justifies this trial on moral and ethical grounds.
Section 9.1: 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.	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 CRPS treatment; inadequate time from*

Changes to this protocol include:	
Formerly read:	**Now reads:**
	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.
Section 9.3.2: Subject discontinuation from the IMP	
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. […]	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).* […]
• 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 <~~30~~ mg/g.	• 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.
• A persistent eGFR <50 mL/min/1.~~73m~~^{2} and urinary ACR >150 mg/g based on repeated quantitative data from the central laboratory, with blood and urine samples obtained at least 1 week apart. ~~• An eGFR <50 mL/min/1.73m^2 and urinary ACR >150 mg/g based on results of the central laboratory or semiquantitative urinary dipstick.~~	• A persistent eGFR <50 mL/min/1.*73 m^2* and urinary ACR >150 mg/g based on repeated quantitative data from the central laboratory, with blood and urine samples obtained at least 1 week apart.
Section 10.1.2: Preparation	
The volume of IMP transferred to the infusion bag must be recorded.	The volume of IMP transferred to the infusion bag must be recorded *in the CRF*.
Section 11.1: Course of the trial	
All visits should be attended in a fasting state (at least 8 hours).	All visits*, except Visit 1,* should be attended in a fasting state (at least 8 hours).
Section 11.1.1.1: Visit 1 (Day -60 to Day -1)	
• ~~Collect~~ urine ~~for~~ drugs of abuse testing.	• *Perform* urine drugs of abuse testing.
Section 12.1: Overview of blood sampling in this trial	
The total blood volume drawn per subject ~~will~~ be ~~approximately 200~~ mL during the trial… […] Table 3: Planned approximate blood sampling volumes collected from each subject […]	The total blood volume drawn per subject *is estimated to* be *less than 180* mL during the trial… […] Table 3: Planned approximate blood sampling volumes collected from each subject […]

Changes to this protocol include:	
Formerly read:	**Now reads:**
~~Serum bicarbonate (EU sites only)~~ ~~(2.5 mL)~~ ~~(11)~~ ~~(27.5 mL)~~ **Total ~~(US sites)~~** **40** **173.5 mL** **~~Total (EU sites)~~** **~~51~~** **~~201 mL~~**	**Total** **40** **173.5 mL**
Section 12.2.3.2: Dental history	
Dental history will include the date of last dental visit; dental extractions and other invasive dental surgery in past ~~12~~ months…	Dental history will include the date of last dental visit; dental extractions and other invasive dental surgery in past *3* months *prior to the Enrollment Visit*…
Section 12.2.4.2: Urine drugs of abuse test	
Urine samples will be provided by the subject at the Enrollment Visit for testing for drugs of abuse ~~. The drugs to be screened for~~ using ~~suitable validated methods (e.g.,~~ dipstick~~) include~~: […] Subjects who are receiving stable doses of prescribed medications containing amphetamines, benzodiazepines, or opioids may participate even if the test is positive.	Urine samples will be provided by the subject at the Enrollment Visit 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 CRF*: […] Subjects who are receiving stable doses of prescribed medications containing amphetamines, benzodiazepines, or opioids may participate *(according to the judgment of the investigator upon approval by the sponsor)* even if the test is positive.
Section 12.3.5: Safety laboratory	
Laboratory tests (except for urine ~~dipstick~~) will be performed by a central safety laboratory. […] Throughout the clinical part of the trial, the investigator must provide ~~feedback~~ regarding the clinical relevance of any laboratory values outside the ~~reference~~ range.	Laboratory tests (except for urine *dipsticks for urine drugs of abuse testing and urine pregnancy testing*) will be performed by a central safety laboratory. […] Throughout the clinical part of the trial, the investigator must provide *a comment in the CRF* regarding the clinical relevance of any laboratory values outside *of* the *sponsor-defined alert* range.

19.4 Protocol amendment 04

Amendment rationale

This amendment is implemented to:

- Increase the size of the target population.
- Clarify the planned number of bone biopsies and bone densitometry and MRI assessments.

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 1.5.1: Sample size rationale	
The sample size is intended to maximize available safety data to support product registration. ~~In combination with subjects receiving active treatment in the ongoing placebo-controlled trial (KF7013-01) and further planned trials of neridronic acid, the number of subjects included in this trial is intended to support regulatory requirements for at least 500 subjects evaluated for safety.~~ It is estimated that approximately 2~~2~~0 subjects will be included in this trial~~; the actual number of subjects allocated, however, may depend on enrollment in ongoing and further planned trials~~.	The sample size is intended to maximize available safety data *in line with the FDA regulatory requirements* to support product registration. It is estimated that approximately 2*9*0 subjects will be included in this trial.
Section 1.6: Schedule of events	
u) ~~B~~one densitometry (DXA) and MRI ~~will be performed~~ in a subset of 30 subjects . v) A single bone biopsy will be obtained from the iliac crest, following tetracycline double-labeling, in a subset of subjects. The biopsy should be scheduled to be performed 26 weeks after the first administration of IMP. ~~Biopsies will be obtained from approximately 20 subjects to obtain 15 evaluable biopsy specimens .~~	u) *It is planned to perform b*one densitometry (DXA) and MRI in a subset of 30 subjects. v) A single bone biopsy will be obtained from the iliac crest, following tetracycline double-labeling, in a subset of subjects. The biopsy should be scheduled to be performed 26 weeks after the first administration of IMP. *It is planned to obtain approximately 15 evaluable bone biopsy samples from approximately 20 subjects.*
Section 8.1: Discussion of the trial design	
Normal bone mineralization and bone formation were observed in biopsies from regions of non-pagetic bone (iliac crest), and improved indices of bone turnover were observed in regions of pagetic bone. ~~Biopsies will be obtained from approximately 20 subjects to obtain 15 evaluable biopsy specimens.~~ It is anticipated that ~~15 evaluable~~ biopsy specimen~~s~~ will ~~be adequate to~~ confirm normal bone mineralization in the iliac crest at approximately 6 months following treatment with neridronic acid 400 mg. A 6 month time point was selected for the biopsy in order to match the slow kinetics of bone matrix and mineral apposition in	Normal bone mineralization and bone formation were observed in biopsies from regions of non-pagetic bone (iliac crest), and improved indices of bone turnover were observed in regions of pagetic bone. *It is planned to obtain approximately 15 evaluable bone biopsy specimens from approximately 20 subjects.* It is anticipated that *bone* biopsy specimen *evaluation* will confirm normal bone mineralization in the iliac crest at approximately 6 months following treatment with neridronic acid 400 mg. A 6 month time point was selected for the biopsy in order to match the slow kinetics of bone matrix and mineral apposition in

Changes to this protocol include:	
Formerly read:	**Now reads:**
humans, with approximately 6 months required to complete a single remodeling cycle (Riggs and Parfitt 2005). ~~A~~ subset of 30 subjects will undergo bone densitometry and MRI to assess the effect of neridronic acid on BMD…	humans, with approximately 6 months required to complete a single remodeling cycle (Riggs and Parfitt 2005). *It is anticipated that a* subset of 30 subjects will undergo bone densitometry and MRI to assess the effect of neridronic acid on BMD…
Section 11.1.1.1: Visit 1 (Day -60 to Day -1)	
• Perform bone imaging (DXA and MRI will be performed in a subset of 30 subjects [from US sites only]).	• Perform bone imaging (DXA and MRI will be performed in a subset of *approximately* 30 subjects [from US sites only]).
Section 11.1.3.4: Visit 9 (Week 26; ±15 days)	
A single bone biopsy will be obtained from the iliac crest, following tetracycline double-labeling, in a subset of subjects (from US sites only). The biopsy should be scheduled to be performed 26 weeks after the first administration of IMP. Biopsies will be obtained from approximately 20 subjects to obtain 15 evaluable biopsy specimens. […] • Perform bone imaging (DXA and MRI will be performed in a subset of 30 subjects [from US sites only]).	A single bone biopsy will be obtained from the iliac crest, following tetracycline double-labeling, in a subset of subjects (from US sites only). The biopsy should be scheduled to be performed 26 weeks after the first administration of IMP. Biopsies will be obtained from approximately 20 subjects to obtain *approximately* 15 evaluable biopsy specimens. […] • Perform bone imaging (DXA and MRI will be performed in a subset of *approximately* 30 subjects [from US sites only]).
Section 14.1.1: Sample size rationale	
Subset of subjects for bone biopsies The sample size is not based on statistical considerations; ~~15 evaluable~~ biopsy specimen~~s are considered adequate to be able to~~ identify qualitative bone abnormalities such as osteomalacia as well as quantitative indicators of impaired mineralization. **Subset of subjects for bone densitometry and magnetic resonance imaging** The sample size is not selected based on statistical considerations. Results from ~~30~~ subjects are considered to be sufficient to demonstrate feasibility and ~~support a rationale for the future use~~ of these assessments in trials of neridronic acid in CRPS.	**Subset of subjects for bone biopsies** The sample size is not based on statistical considerations; *bone* biopsy specimen *evaluation will* identify qualitative bone abnormalities such as osteomalacia as well as quantitative indicators of impaired mineralization. **Subset of subjects for bone densitometry and magnetic resonance imaging** The sample size is not selected based on statistical considerations. Results from *this subset of* subjects are considered to be sufficient to demonstrate feasibility and *explore outcomes* of these assessments in trials of neridronic acid in CRPS.