kf7013-04 SAP

NCT03560986

ELECTRONIC SIGNATURES

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STATISTICAL ANALYSIS PLAN

Trial code:	KF7013-04
Title of trial:	Placebo-controlled efficacy and safety trial of intravenous neridronic acid in subjects with complex regional pain syndrome (CRPS)
EudraCT number:	2017-004244-37
Universal Trial Number:	U1111-1203-5020
Development phase:	Phase III

Final Version	Date	DMS version number
	08 Jun 2018	1.0

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2 ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse event
ANCOVA	Analysis of covariance
ß-HCG	Beta-human chorionic gonadotropin
BAP	Bone alkaline phosphatase
BMI	Body mass index
CI	Confidence interval
CIR	(Crude) Incidence rate
CRPS	Complex regional pain syndrome
CV	Coefficient of variation
DMA	Dynamic mechanical allodynia
ECG	Electrocardiogram
EQ-5D-5L	EuroQoL-5 Dimension-5 level
FAS	Full Analysis Set
ICTR	Integrated clinical trial report
IMP	Investigational medicinal product
N	Number of subjects in population
NRS	Numerical rating scale
MAR	Missing at random
Max	Maximum
MNAR	Missing not at random
Min	Minimum
Q1	First quartile
PCS	Pain Catastrophizing Scale
PDS	Pharmacodynamic Set
PGIC	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PMI	Placebo multiple imputation
PMM	Pattern mixture model
PSEQ	Pain Self Efficacy Questionnaire
PT	Preferred Term
Q3	Third quartile
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	Relative risk
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical analysis plan
SAS	Statistical analysis software

Abbreviation	Explanation
SD	Standard deviation
TEAE	Treatment emergent adverse event
VAS	Visual analog scale
WPAI	Work Productivity and Activity Impairment Questionnaire

Système International d'Unités units are not included in this list.

3 INTRODUCTION

This statistical analysis plan (SAP) includes all definitions and analysis details for the analysis of the trial in accordance with the protocol dated 14 Mar 2018. The analysis will be performed by the sponsor in accordance with this SAP.

4 TRIAL OBJECTIVES

Objective	Endpoint/Outcome	Measure description and timeframe
Primary To demonstrate the superior efficacy of a cumulative dose of 400 mg intravenous neridronic acid versus placebo for the treatment of CRPS-related pain.	**Primary** Change from baseline to Week 12 in the average pain intensity score (weekly average of pain values recorded daily in the electronic diary).	**Primary** 11-point numerical rating scale (NRS)—from 0 = "no pain" to 10 = "pain as bad as you can imagine" —reported once daily (in the evening, 24-hour recall) in an electronic diary. The change from the baseline phase (Day -7 to Day -1) to Week 12 will be analyzed.
Secondary	**Secondary**	**Secondary**
To assess the efficacy of a cumulative dose of 400 mg intravenous neridronic acid versus placebo for the treatment of CRPS-related pain.	Change from baseline to Week 26 in the average pain intensity recorded on the tablet computer.	11-point NRS—from 0 = "no pain" to 10 = "pain as bad as you can imagine"—reported at the visits on a tablet computer (24-hour recall). The change from baseline (Visit 2 [Day 1]) to Visit 11 (Week 26) will be analyzed.
	Pain response to treatment, defined as at least 30% decrease from baseline in the average pain intensity at Week 12, recorded on the tablet computer.	11-point NRS—from 0 = "no pain" to 10 = "pain as bad as you can imagine"—reported at the visits on a tablet computer (24-hour recall). The change from baseline (Visit 2 [Day 1]) to Visit 8 (Week 12) will be analyzed.
	Pain response to treatment, defined as at least 30% decrease from baseline in the average pain intensity at Week 26, recorded on the tablet computer.	11-point NRS—from 0 = "no pain" to 10 = "pain as bad as you can imagine"—reported at the visits on a tablet computer (24-hour recall). The change from baseline (Visit 2 [Day 1]) to Visit 11 (Week 26) will be analyzed.

Objective	Endpoint/Outcome	Measure description and timeframe
To assess the efficacy of a cumulative dose of 400 mg intravenous neridronic acid versus placebo on the dynamic mechanical allodynia (DMA).	Change from baseline to Week 12 in the pain intensity level of DMA.	Dynamic mechanical allodynia: a tactile stimulus is applied in a single sweeping motion (1 cm to 2 cm length) on the skin on the affected limb. The subjects are asked to judge the stimulus intensity by means of an NRS (0 to 10). "0" in this case means "no pain". Each "pricking", "stinging" or "burning" sensation is defined as a painful sensation, which should always be evaluated by giving a value greater than "0". "10" corresponds to the individual maximum pain imaginable. The change from baseline (Visit 2 [Day 1]) to Visit 8 (Week 12) will be analyzed.
To assess the efficacy of a cumulative dose of 400 mg intravenous neridronic acid versus placebo on the pressure pain threshold (PPT).	Change from baseline to Week 12 in the PPT ratio for the thenar muscle/abductor hallucis muscle.	Pressure pain threshold: using a pressure algometer (contact area 1 cm^2), the threshold for pressure-induced pain is measured on the thenar muscle/abductor hallucis muscle in 3 series of slowly increasing stimulus intensities (at a rate of about 50 kPa/s). The threshold is then determined as the arithmetic mean of the 3 series (in kPa). The ratio of the thresholds of the affected limb versus the unaffected limb will be calculated. The change from baseline (Visit 2 [Day 1]) to Visit 8 (Week 12) will be analyzed.
To assess the efficacy of a cumulative dose of 400 mg intravenous neridronic acid versus placebo on edema of the hand or foot.	Change from baseline to Week 12 in the ratio of the figure of eight measurements of the affected limb versus the unaffected limb.	In subjects with the CRPS sign of edema on the CRPS Severity Score at baseline, circumference of the hand or foot will be measured by the investigator with measurement tape using the figure-of-eight method at both the affected limb and the contralateral unaffected limb. Each measurement will be performed 3 times. The average of the 3 measurements will be used for further analysis. The ratio of the averages of the affected limb versus the unaffected limb will be calculated. The change from baseline (Visit 2 [Day 1]) to Visit 8 (Week 12) will be analyzed.

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

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

To assess the efficacy of neridronic acid in subjects with CRPS

- Change from baseline to Week 52 in average pain intensity recorded on the tablet computer.
- Change from Week 26 to Week 52 in average pain intensity recorded on the tablet computer.
- Pain response to treatment, defined as at least 50% decrease from baseline in the average pain intensity at Week 52, based on pain intensity recordings on the tablet computer.
- Pain response to treatment, defined as at least 50% decrease from Week 26 in the average pain intensity at Week 52, based on pain intensity recordings on the tablet computer.
- Pain response to treatment, defined as at least 50% decrease from baseline in the average pain intensity at Week 12, based on pain intensity recordings on the tablet computer.
- Pain response to treatment, defined as at least 50% decrease from baseline in the average pain intensity at Week 26, based on pain intensity recordings on the tablet computer.
- Pain response to treatment, defined as at least 30% decrease from baseline in the average pain intensity at Week 52, based on pain intensity recordings on the tablet computer.
- Pain response to treatment, defined as at least 30% decrease from Week 26 in the average pain intensity at Week 52, based on pain intensity recordings on the tablet computer.
- Change from baseline to Week 12 in pain intensity scores determined using worst and current pain ratings recorded daily in the electronic diary.
- Change from baseline to Week 26 in worst and current pain intensity ratings, recorded on the tablet computer.
- Change from baseline to Week 52 in worst and current pain intensity ratings, recorded on the tablet computer.
- Change from Week 26 to Week 52 in worst and current pain intensity ratings, recorded on the tablet computer.
- Change from baseline to Week 6, Week 26, Week 36, and Week 52 in the pain intensity level of DMA.
- Change from baseline to Week 6, Week 26, Week 36, and Week 52 in PPT ratios.
- Change from baseline to Week 6, Week 26, Week 36, and Week 52 in the ratio of the figure of eight measurements of the affected limb versus the unaffected limb.
- Change from baseline to Week 6, Week 12, Week 26, Week 36, and Week 52 in the active range of motion (AROM) ratio (affected limb and unaffected limb) measured in the hand or foot, respectively.
- Change from baseline to Week 12, Week 26, and Week 52 in the CRPS Severity Score.
- Patient Global Impression of Change (PGIC) at Week 6, Week 12, Week 16, Week 22, Week 26, Week 28, Week 36, and Week 52.
- Change from baseline to Week 6, Week 12, Week 16, Week 22, Week 26, Week 28, Week 36, and Week 52 in the Patient Global Impression of Severity (PGI-S).
- Change from Week 26 to Week 52 in the PGI-S.
- Change from baseline to Week 12 and Week 26 in the EuroQoL-5 Dimension-5 level (EQ-5D-5L) index score and the health-related visual analog scale (VAS) score.
- Change from baseline to Week 52 in the EQ-5D-5L index score and the health-related visual analog scale score.
- Change from Week 26 to Week 52 in the EQ-5D-5L index score and the health-related visual analog scale score.
- Change from baseline to Week 6, Week 12, Week 26, Week 28, Week 36, and Week 52 in the responses to

questions on the following questionnaires (recorded on the tablet computer):

- Patient-Reported Outcomes Measurement Information System (PROMIS®)-29 profile version 2.0 (PROMIS-29 profile) (sub-scores: physical function, anxiety, depression, fatigue, sleep disturbance, social roles and activities, and pain interference). The change from baseline to Week 16 and Week 22 will be assessed for question number 29, GLOBAL07 only.
- Question EDDEP39 of the PROMIS Item Bank version 1.0 – Emotional Distress – Depression (PROMIS-EDDEP39).
- The 6 neuropathic pain items of the Short-Form McGill Pain Questionnaire 2 (SF-MPQ-2) (single items and the combined score).
- Pain Catastrophizing Scale (PCS).
- Pain Self Efficacy Questionnaire (PSEQ).

To describe the trial population and to evaluate subject eligibility

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

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

- Adverse events, concomitant medications, physical examination findings, 12-lead electrocardiograms (ECGs), vital signs, body weight, and safety laboratory data.

To assess the pharmacodynamics of neridronic acid in subjects with CRPS

- Concentrations of bone turnover markers in serum: (C-terminal telopeptide of type I collagen [CTX], bone alkaline phosphatase [BAP], and procollagen type I amino-terminal propeptide [PINP]).

To assess health economics and work productivity (US sites only)

- Work Productivity and Activity Impairment Questionnaire: CRPS (WPAI: CRPS).
- Medical resources utilization.

To explore markers for disease severity or progression in CRPS

- Concentrations of soluble interleukin-2 receptor (sIL-2R).

5 TRIAL DESIGN

5.1 Overall trial design and plan

Only a brief synopsis of the trial design is presented here; full details can be found in the trial protocol.

This is a multi-site, randomized, double-blind, placebo-controlled, 2-arm, Phase III trial of intravenous neridronic acid in subjects with complex regional pain syndrome (CRPS). The trial will consist of two treatment periods, Treatment Period A will be double-blind whereas Treatment Period B will be open-label. However, investigators and subjects will remain blinded to their initial treatment.

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

At Visit 11 (Week 26), subjects not meeting the pre-specified criteria to continue into Treatment Period B will continue in Follow-up Period 2 until Visit 17 (Week 52). Subjects meeting the pre-

specified criteria will enter the open-label Treatment Period B with 4 additional infusions over 10 days and follow-up visits until Visit 17 (Week 52).

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

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

For subjects with no or mild renal impairment in Treatment Period A, the full contents of a single vial will be administered at Visit 2, Visit 3, Visit 4, and Visit 5, resulting in a total dose of 400 mg neridronic acid or matching placebo.

For subjects with no or mild renal impairment included in Treatment Period B, the full contents of a single vial will be administered at Visit 11, Visit 12, Visit 13, and Visit 14, resulting in a total dose of 400 mg neridronic acid.

Dose adaptations will be made in case of moderate renal impairment resulting in total doses of 250 mg (CKD-EPI Stages 3b) or 300 mg neridronic acid (CKD-EPI Stages 3a).

5.2 Sample size

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

For a difference in the means of $\mu 400 - \mu 0 = -1.0$ points on the NRS, assuming a standard deviation of 2.0 points on the NRS and a 1-sided significance level of 2.5% ($\alpha = 0.025$), 86 subjects per arm will be required to provide at least 90% power ($1-\beta = 0.9$) to reject the null hypothesis. To compensate for a slight decrease in power due to an optional futility interim analysis, a total of 180 subjects (90 subjects per arm) are planned to be allocated to treatment.

5.3 Randomization

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

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

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

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

6 OVERVIEW OF PLANNED ANALYSES

6.1 Final analysis

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

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

6.2 Interim analyses

An interim analysis is planned after a combined total of approximately 80 subjects in the 2 Phase III trials, KF7013-02 and KF7013-04, have completed Week 12 of treatment and the data is available in the databases. The interim analysis is for futility only and will be non-binding. The futility criterion will be based on the unblinded comparison of the primary endpoint and will be calculated using identical methods as for the final analysis. If the observed difference in the means of $\mu 400 - \mu 0$ is ≥ -0.3 points on the NRS, the null hypothesis will not be rejected and the recommendation will be to stop both trials. The interim analysis will be performed by an independent statistical analysis unit not otherwise involved in the conduct of the trial and the result will only state the recommendation to stop or continue the Phase III program. No unblinded information will be disseminated to the trial teams. Pending recruitment rates of both trials, it may be decided to forgo the interim analysis or conduct it a different point in time. As the interim analysis will be for futility only, no inflation of the type I error will occur.

The interim analysis will be further described in a separate SAP as it will be performed on the pooled data of 2 trials.

7 DOCUMENT AND CHANGE HISTORY

7.1 Changes in analysis compared to the trial protocol

Not applicable.

Change from protocol	Rationale for change
Section 1.2 Trial objectives, endpoints, and outcomes **Other data to be collected that are not directly attributed to or considered as an endpoint** • Change from baseline to Week 6, Week 12, Week 26, Week 28, Week 36, and Week 52 in the responses to questions on the following questionnaires (recorded on the tablet computer): – Patient-Reported Outcomes Measurement Information System (PROMIS®)-29 profile version 2.0 (PROMIS-29 profile) (sub-scores: physical function, anxiety, depression, fatigue, sleep disturbance, social roles and activities, and pain interference). The change from baseline to Week 16 and Week 22 will be assessed for question number 29, GLOBAL07 only. – Question EDDEP39 of the PROMIS Item Bank version 1.0 – Emotional Distress – Depression (PROMIS-EDDEP39*) (not for Week 28)*. – The 6 neuropathic pain items of the Short-Form McGill Pain Questionnaire 2 (SF-MPQ-2) (single items and the combined score). – Pain Catastrophizing Scale (PCS) *(not for Week 28)*. – Pain Self Efficacy Questionnaire (PSEQ) *(not forWeek 28)*.	Schedule of events in protocol shows that these assessments are not done at Week 28.
Protocol Section 14.1.7.2 Analysis of the secondary endpoints A logistic regression model will be fitted to the data, including the covariate baseline pain intensity score, and the factors geographic region, week, and treatment, and treatment-by-week interaction as fixed effects.	Change to logistic regression at respective weeks instead of longitudinal analysis to simplification of model fitting.

7.2 SAP amendment rationale

Not applicable.

8 ANALYSIS CONVENTIONS

8.1 General principles

All presentations will be done by treatment group.

Presentation of treatment groups will differ for the Week 1 to Week 26 and Week 27 to Week 52. Treatment groups for Week 1 to Week 26 are Placebo and Neridronic acid 400mg. For presentation of Week 27 to Week 52 in the final report, subjects will be displayed based on their treatment in Treatment Period A Placebo and Neridronic acid 400 mg and whether they have been treated with neridronic acid in Treatment Period B. Hence, for the final report, 4 treatment arms will be presented: Placebo, Placebo + Treatment Period B, Neridronic acid 400 mg and Neridronic acid 400mg + Treatment Period B and, if applicable, information will be summarized in an overall group.

The results from the 26-week analysis will be reported in an interim integrated clinical trial report. The display of the efficacy results in this report will be limited to all data up until Visit 11/Week 26, safety data will be reported for all data until the respective cut-off date. For the final ICTR, TFLs and analysis will be extended and additionally all data assessed after Visit 11/Week 26 will be analyzed and displayed.

The data collected and derived in the trial will be presented in subject data listings sorted by site and treatment.

Data collected in this trial will be summarized according to their nature as follows if not specified otherwise:

- Continuous variables: number of non-missing observations, arithmetic mean, standard deviation, minimum and maximum values, median and quartiles. If there are less than 5 observations, descriptive statistics will be presented based on the rules specified in Section 19.1.1.2.
- Categorical variables: absolute and relative frequencies. If not defined otherwise, the percentage denominator will be the number of subjects still in the trial (including missing values) at the respective time point in the analyzed population. The category missing will only be displayed if missing values occur.
- Time-to-event variables: Kaplan-Meier estimates together with the 95% confidence intervals (CI) and the hazard rate will be provided with the respective number at risk and the number censored at the relevant time points. In addition, the median time-to-event and its 95% CI will be presented if applicable. For calculating the survival estimate CI bounds, the log-log transformed estimate of CI bounds will be used. The time to event will be censored at the Visit 11 for the Week 26 report and End-of-Treatment Visit/End-of-Trial Visit for the final report if not otherwise specified.

Medical terms (e.g., prior and concomitant diseases, adverse events) will be coded via Medical Dictionary for Regulatory Activities (MedDRA). For the analysis, the primary System Organ Class SOC will be used. Medications will be coded according to World Health Organization Drug Dictionary (WHO-DD).

Table 1 shows the use of analysis sets in different analyses as defined in Section 9.

Table 1: Use of analysis sets

	Enrolled Set	Allocated Set	SAF	FAS	PDS
Subject disposition	X	X	X	X	
Discontinuations	X	X	X	X	
Protocol deviations			X		
Demographics			X	X	
Other baseline characteristics			X	X	
Subject medical and dental history			X	X	
CRPS history			X	X	
Prior and concomitant medication			X	X	
Exposure			X		
Compliance			X		
Primary endpoint				X	
Secondary endpoint				X	
Adverse events			X		
Laboratory values			X		
Bone turnover markers					X
Soluble interleukin-2 receptor (sIL-2R)			X		
Other safety parameter			X		

FAS = Full Analysis Set, PDS = Pharmacodynamic Set, SAF = Safety Analysis Set

8.2 Definitions

8.2.1 Definition of subgroups

The following subgroups will be analyzed:

- Gender (male, female).
- Age (<65, >= 65).
- Region (USA/Canada, Europe, and Other Regions [including Asia-Pacific and Australia/New Zealand]).

Subgroup analyses will be limited to the primary endpoint and disposition and demographic information.

8.2.2 Further definitions

Baseline	Baseline is defined as the last observation (scheduled or unscheduled) before first IMP administration if not otherwise specified. In general, baseline is the value recorded at Visit 2. More precisely, for post-baseline comparisons of all parameters except pain intensity in the eDiary, the assessment before first IMP administration at Visit 2 (Day 1) will serve as the baseline based on recorded date/times. In case the value planned on Day 1 is missing or in case there are multiple values before first IMP administration on Day 1, the last scheduled or unscheduled non-missing value before first IMP administration will be used. For current, average, and worst pain, baseline pain intensity will be calculated as the average of the non-missing pain intensity ratings obtained over the 7-day baseline pain assessment phase prior to first IMP administration.
Investigational Medicinal Products (IMP)	The IMPs used in this trial are neridronic acid and matching placebo.
On-treatment-period	For the purpose of this trial, the on-treatment period starts at the first IMP administration (included) and continues until the date (included) when the subject leaves the trial, i.e., at the Final Visit (Visit 17, week 52 after Follow up period 2) for trial completers, and otherwise at the End of Trial date for subjects not fully completing the trial. The on-treatment period extends beyond the dosing period. This is because of the persistence in bone and potentially prolonged effect of neridronic acid.
Pooling of sites	Individual sites will be pooled by geographic region. Geographic regions are defined as USA/Canada, Europe, and Other Regions (including Asia-Pacific and Australia/New Zealand).
Pre-treatment-period	Before the first IMP administration (excluded).
Treatment Period A completers	Treatment Period A completers are treated subjects who completed IMP administration in Treatment Period A according to the protocol, i.e., subjects who received the full dose of all 4 planned infusions. Subjects are identified via the “Treatment Period A completer” page in the CRF based on the data point “Did the subject complete the treatment?”
Follow-up Period 1 completers	Follow-up Period 1 completers are treated subjects who completed the Follow-up Period according to the protocol, i.e., subjects who have a Visit 11 not before Day 183. Subjects do not need to be Treatment A completers.

Treatment Period B completers	Treatment Period B completers are treated subjects who completed IMP administration in Treatment Period B according to the protocol, i.e., subjects who received the full dose of all 4 planned infusions. Subjects are identified via the "Treatment Period B completer" page in the CRF based on the data point "Did the subject complete the treatment?"
Follow-up Period 2 completers	Follow-up Period 2 completers are treated subjects who completed the Follow-up Period 2 according to the protocol, i.e., subjects who have a Visit 17 not before Day 365. Subjects do not need to be Treatment Period A or Treatment Period B completers.
Trial completers	Trial completers are treated subjects who completed the trial according to the protocol. Subjects are identified via the End of Trial page in the CRF based on the data point "Trial fully completed?" Subjects do not need to be Treatment Period A or Treatment Period B completers to fully complete the trial.

9 SUBJECT POPULATIONS

9.1 Enrolled Set

The Enrolled Set includes all subjects who signed the informed consent form.

9.2 Allocated Set

The Allocated Set includes all subjects who are allocated to treatment. Presentation of the Allocated Set will be conducted according to the allocated treatment.

9.3 Safety Set

The Safety Set (SAF) includes all subjects with at least 1 IMP administration including any partial infusion.

Analysis on the SAF will be conducted on the actual treatment received. Subjects that by accident switched treatment arm during the trial will be assigned to one treatment arm before unblinding.

9.4 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects allocated with at least 1 IMP administration, including any partial infusion.

Analysis on the FAS will be conducted according to the allocated treatment.

9.5 Pharmacodynamic Set

The Pharmacodynamic Set (PDS) defines all treated subjects with at least 1 non-missing value for at least 1 of the bone turnover markers.

10 DISPOSITION

10.1 Subject disposition

All presentations for subject disposition will be by treatment group and overall.

For describing the subject disposition, the following populations will be summarized, overall and for the following subgroups: gender, region and age group:

- Display with percentage denominator being the number of enrolled subjects.
  - Subjects enrolled (only overall).
  - Subjects enrolled but not allocated and reason for non-allocation (only overall).
- Displayed with percentage denominator being the number of allocated subjects. For the reasons for not being treated for subjects allocated but not treated, the percentage denominator is the number of allocated but not treated.
  - Subjects allocated (=Subjects allocated to Treatment Period A).
  - Subjects allocated but not treated and the reasons for not being treated.
  - SAF.
  - FAS.
  - Pharmacodynamic Set.
  - Treatment Period A completers.
  - Follow-up Period 1 completers.
  - Treated in Treatment Period B.
  - Treatment Period B completers.
  - Follow-up Period 2 completers.
  - Trial completers treated only in Treatment period A.
  - Trial completers.
  - Subjects allocated and discontinued from IMP in Treatment Period A.
  - Subjects allocated and discontinued from the trial in Treatment Period A.
  - Subjects allocated and discontinued from the trial.
- Displayed with percentage denominator being the number of subjects allocated in Treatment Period B:
  - Subjects allocated in Treatment Period B.
  - Subjects allocated and treated in Treatment Period B.
  - Subjects allocated in Treatment Period B but not treated and the reasons for not being treated.
  - Treatment Period B completers.
  - Trial completers treated in treatment Period B.
  - Trial completers.
  - Subjects allocated and discontinued from IMP in Treatment Period B.
  - Subjects allocated and discontinued from the trial in Treatment Period B.

In addition, an overview table will be prepared presenting the number of subjects enrolled, allocated, in the SAF, and in the FAS per country and per site. Percentage calculation will be done in 2 ways:

- Denominator will be the number of all allocated subjects.
- Denominator will be the number of allocated subjects in the respective country and site.

10.2 Subject discontinuations

Discontinuations from the trial and from IMP will be presented for the SAF overall, per country and per site.

Reasons for discontinuations from the trial or from IMP will be presented for:

- Subjects discontinued from the trial.
- Subjects discontinued from IMP in Treatment Period A.
- Subjects discontinued from IMP in Treatment Period B.

Percentage denominator will be the number of subjects discontinuing in the respective group.

The details for "other reasons" will be presented in a frequency table, if applicable.

If more than 10% of subjects in the SAF discontinue the trial, the distribution of the time to discontinuation from the trial will be summarized using time-to-event methods. Time will be weeks until discontinuation.

10.3 Protocol deviations

Major protocol deviations will be presented overall and by site for the SAF. They will be grouped into categories as collected and summarized descriptively.

Major protocol deviations will be presented in a subject data listing sorted by site and treatment.

11 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

No statistical tests for comparison of demographic and baseline data between treatment groups will be performed.

Subject demographics and baseline characteristics will be summarized descriptively by treatment group and overall.

Subject demographics and other baseline characteristics will be descriptively summarized for the SAF and the FAS. Subject demographics will also be presented for the enrolled set; presentation will be without treatment group but only for overall.

Furthermore, the subgroups will be displayed as defined in Section 8.2.1.

11.1 Subject demographics

Subject demographics are age [years], height [m], sex, race, ethnicity, and age group.

Age groups will be <18 years, ≥18 years and <65 years, ≥65 years and <85 years, and ≥85 years.

Remark:

Weight is recorded several times together with the vital signs parameters. Therefore, weight and the derived body mass index (BMI) will be described in the vital signs section below.

11.2 Other baseline characteristics

For parameters collected on more than 1 occasion during the trial including baseline, the assessment at baseline will be presented together with the assessments collected later in the trial rather than in a separate table for the baseline assessment only. These parameters are:

- Efficacy outcome parameters, e.g., pain intensities (current, average, and worst).
- Questionnaires and CRPS severity score (including signs and symptoms of CRPS).
- Laboratory parameters.
- Twelve-lead ECG parameters.
- Vital signs parameters.
- Bone turnover markers.
- Soluble interleukin-2 receptor.

11.3 Subject medical history

11.3.1 Medical history

Diseases and surgical interventions are presented as “prior” or “concomitant” as documented by the investigator.

Medical history will be summarized and sorted alphabetically, separately for prior and concomitant diseases, by SOC and Preferred Term (PT). The number of subjects will be displayed for each SOC and PT.

11.3.2 Dental history

Dental history will be summarized separately in the same way as the medical history.

Furthermore, the time since the last dental visit will be summarized.

11.3.3 Complex regional pain syndrome (CRPS) history

CRPS history will be descriptively summarized:

Continuous parameters based on date of Visit 1are:

- Time since inciting or precipitating event (month) – if unknown presented as unknown.
- Time since onset of CRPS symptoms (month).
- Time since diagnosis of CRPS (month).

Categorical baseline characteristics are:

- CRPS type (Type I, Type II, Unknown).
- CRPS etiology.
  - Inciting or precipitating event (Missing, Known, Unknown).
  - Fracture, Sprain, Surgery, Crush, Others.

- CRPS location (Left Body Site, Right Body Site, Upper Extremity, Lower Extremity, more than 1 Limb affected).
- CRPS family history.
  - CRPS family history (No, Yes, Unknown).
  - Same limbs (No, Yes, Unknown).
- Imaging method (None, Unknown, X-rays, Magnetic resonance imaging (MRI), Triple-phase bone scintigraphy, Other).

Except for inciting or precipitating event and family history multiple answers are possible.

11.4 Prior and concomitant medication or therapy

Prior and concomitant therapies will be descriptively summarized by category of additional therapy/treatment. Assessment of prior and concomitant will be done as described in the following for medications.

Prior and concomitant medication is collected in the e-CRF as per enrollment. For the analysis, the following algorithm will be used to define prior and concomitant medication:

- Prior is all medication stopped prior to the first dose of IMP, regardless of its start date.
- Concomitant is any medication not stopped before the first dose of IMP, regardless of its start date or medication started after the first dose of IMP.

Medication will be summarized and sorted alphabetically separately for prior and concomitant medication by Anatomical Therapeutic Chemical categories (Level 2: pharmacological or therapeutic subgroup and Level 3: chemical or therapeutic or pharmacological subgroup).

For each medication, the number of subjects will be displayed.

Medication or therapy started after last dose of IMP will be flagged in the subject data listing.

In addition, all newly prescribed opioid analgesic medication will be separately summarized overall and up to Week 26. Furthermore, the time to first newly prescribed opioid analgesic medication after first IMP will be summarized using time-to event methods. A newly prescribed opioid analgesic medication is any medication that is started after first IMP.

12 EXPOSURE AND COMPLIANCE

Exposure and compliance will be descriptively summarized for the SAF.

12.1 Exposure

Exposure will be displayed for both treatment periods as the number of subjects receiving 1,2,3 or 4 infusions. It will be descriptively summarized. For percentage calculation, the denominator will be the number of subjects in the FAS for the Treatment Period A. For the Treatment Period B, the denominator will be the number of subjects treated in Treatment Period B.

In addition, 2 further overviews will be generated.

First the number of subjects with a planned reduced dose will be summarized. Those subjects are identified if the eCRF entry "Volume of drug transferred into the infusion bag" is not 8 mL. Denominator usage as described above.

Secondly, the number of subjects with a completely and not completely administered dose will be displayed. The display will be done by day for Treatment Period A (Day 1, Day 4, Day 7, Day 10) and visit for Treatment Period B (Visit 11, Visit 12, Visit 13, Visit 14). For percentage calculation, the number of subjects with an administered drug for that day/visit will be used.

12.2 Compliance

Compliance will be assessed for each visit. Compliance (%) to IMP administration will be set to 100%, if the dose was completely administered. Otherwise, compliance (%) will be calculated as the ratio of the approximate value administered, divided by the planned dose (500 mL).

Moreover, the cumulative compliance per treatment period will be derived as the ratio of the actual cumulative dose divided by the planned cumulative dose.

Compliance and cumulative compliance will be descriptively summarized.

13 EFFICACY ANALYSES

13.1 Primary endpoint

13.1.1 Average pain intensity (recorded in the eDiary)

The primary efficacy variable is the change from baseline to Week 12 in the average pain intensity score. The average pain intensity score is calculated as the weekly average of the pain intensities recorded daily (in the evening) in the electronic diary with a 24-hour recall period.

The average pain intensity score for Week *x* is based on the respective 24-average pain intensity scores recorded daily in the electronic diary during week *x*, i.e. 7-day intervals starting Day 1 to Day 7 for Week 1, and Day 8 to Day 14 for Week 2, etc.

For the average pain intensity score for Week *x*, all available values in Week *x* will be used, no imputation will be done for missing scores. If no pain scores are available for a week, the weekly mean for that patient and week will remain missing. E-Diary data beyond Day 84 will not be used for the analysis but be part of the subject data listing. Subjects in the FAS without baseline value and subject without any weekly average pain intensity subject be imputed with zero as change from baseline and for the baseline value imputation will be done as the average baseline value of the treatment arm.

Baseline is calculated as the mean of the average pain intensity score recorded daily in the electronic diary during the baseline phase (Day -7 to Day -1).

13.1.2 Main analysis

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

The primary estimand will be estimated by the analysis of the primary efficacy endpoint for the Full Analysis Set. The primary analysis will fit a mixed model repeated measurement (MMRM) to the change from baseline in the average pain intensity scores from Week 1 to Week 12 recorded once daily in the electronic diary, including the covariate baseline pain intensity score, and the factors geographic region, week, treatment, and treatment-by-week interaction as fixed effects, and subject as random effect. An unstructured covariance matrix will be used to model the covariance structure, degrees of freedom will be estimated using the Kenward-Roger approximation.

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

If the default Newton-Raphson algorithm used by statistical analysis software (SAS) PROC MIXED fails to converge, the Fisher scoring algorithm up to iteration 2 will be used (via the SCORING=2 option of the PROC MIXED statement) to obtain the initial values of covariance parameters (Mallinckrodt et al. 2008). If this alternative also fails to converge, then in addition the no-diagonal factor analytic structure (via the TYPE=FA0(T) option of the REPEATED statement, where T=12 is the total number of weeks in the 12-week trial period) will be used, which effectively performs the Cholesky decomposition of the covariance matrix and is numerically more stable. The first algorithm that leads to convergence in this sequence of fallback measures will be the algorithm used for the primary analysis of the trial.

A descriptive summary of the weekly averages and the changes from baseline will be generated by treatment group.

A graphical plot of the model-based estimates and the 95% CI of the change from baseline of the average pain intensity scores over the 12-week trial period will be created. Both treatments will be presented in one plot by week.

13.1.3 Sensitivity analysis

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

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

Missingness assumptions – considerations

The primary analysis using the MMRM is based on the Missing at Random (MAR) assumption. For the treatment policy or de facto estimand, the MAR assumption is justified for neridronic acid owing to the long half-life in bone and the anticipated persistent effect over the 12-week trial period. It can be assumed that the effect of neridronic acid continues after the treatment period is completed, and it also persists after the treatment period regardless of trial completion or early discontinuation. Therefore, the response of discontinued subjects will not change if the subjects continue to receive the stable therapy that they receive during the 12-week trial period up to Visit 8. If subjects change their treatment after discontinuation from the trial, it is nevertheless reasonable to

assume that their response is not significantly altered as there are currently no established effective treatments. Hence, the MAR assumption is considered a plausible missingness mechanism for the primary estimand in the case of neridronic acid.

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

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

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

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

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

Sensitivity analysis

Sensitivity analyses will be conducted with two imputation methods followed by an analysis of covariance (ANCOVA) model. The ANCOVA model will be fitted to the change from baseline in the average pain intensity scores at Week 12 recorded once daily in the electronic diary, with the covariate baseline pain intensity score, and the factors geographic region and treatment as fixed effects.

The results of the primary analysis and both sensitivity analyses will be summarized numerically and graphically in a forest plot, presenting the number of subjects, model estimates and 95% CIs of the treatment differences to placebo for both active doses.

The primary efficacy analysis will use the observed values of the primary efficacy endpoint without any imputations. To perform the sensitivity analyses for the primary analysis, weekly average pain intensities of the primary efficacy endpoint will be imputed until Week 12.

In the following the concept of PMM will be described as well as the details on the specific PMM imputation information for PMI and the delta shift method.

Pattern mixture models

Subjects dropping out will be classified into patterns according to the week they discontinue from the trial. In each pattern, the distribution of missing values conditional on observed values is determined based on the imputation method used and imputations are drawn from the modified distribution.

The pattern mixture model framework (e.g., Verbeke and Molenberghs 2009) will be implemented using multiple imputation. Multiple imputation comprises 3 separate steps:

1. Impute: Generate *M* completed datasets (week 1 to week 12) drawing imputed values from the pattern-specific distributions. In total *M* = 200 imputations will be generated. This is in line with recommendations in Carpenter and Kenward (2013).
2. Analyze: Analyze the M completed datasets individually (analysis via ANCOVA).
3. Combine: Combine the results from the M individual analyses into a single result using Rubin's rules (Little and Rubin 2002).

The imputation model will be based on the Markov chain Monte Carlo (MCMC) method for general patterns of missingness (Dmitrienko et al. 2005).

The imputations step 1. is described for both PMM used in this trial in the below with the specific imputation used.

All missing values will be imputed in the same way, i.e., no differentiation between intermittent missing values and missing values after dropout is made. Missing values will be imputed for all 12 weeks.

Placebo Multiple Imputation

The Placebo Multiple Imputation method draws imputations in all treatment arms based on the data observed in the placebo arm. In each pattern, the distribution of missing values conditional on observed values is defined for all arms by the corresponding distribution from the placebo arm. The imputation step will be performed as follows:

a. Estimate *M* sets of parameters for the pattern specific reference distribution from the placebo arm. All *M* parameter datasets will be stored in an analysis dataset.
b. Generate *M* completed datasets for all treatment arms using the *M* sets of parameters from step 1. All *M* imputed datasets will be stored in an analysis dataset.

Delta Shift Method

The Delta Shift Method is based on the observed distribution and shifts the observed means at the time points after dropout by a pre-specified value. In each pattern, the distribution of missing values conditional on observed values is based on the shifted means, and imputations are drawn from the modified distribution. This approach models a diminishing placebo effect after a subject drops out.

The sensitivity analysis will use different values for the shift parameter Δ. Delta will start with 0 and be increased by 0.1 points until the tipping point has been reached. The tipping point is defined as the delta that must be added in order to overturn conclusions from the primary analysis from

statistically significant to statistically insignificant. Starting with 0 enables to evaluate MI under the MAR assumption.

The shift parameter is constant, i.e., the same shift parameter will be used for all treatment arms, for all times after dropout, and for all patterns. Based on this, the imputation step will be performed as follows:

a. Estimate *M* sets of parameters of the linear model. All *M* parameter datasets will be stored in an analysis dataset.
b. Generate *M* completed datasets using the *M* sets of parameters from step 1.
c. Modify the completed datasets by adding a shift Δ to each imputed value. All *M* imputed datasets will be stored in an analysis dataset.

All missing values will be imputed in the same way, i.e., no differentiation between intermittent missing values and missing values after dropout is made.

13.2 Secondary endpoints

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

Descriptive summaries will be generated for all visits where data is assessed as per schedule of events in Section 1.7 of the protocol. Analysis will be presented per visit and treatment if not specified differently.

13.2.1 Average pain intensity (recorded on tablet computer)

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

The analysis will be performed using the contrast, i.e., the mixed model Wald test, of 400 mg neridronic acid versus placebo at Week 26 of the treatment, week and treatment-by-week interaction term of the mixed effects model described above. Model-based parameter estimates, standard errors, 95% confidence intervals, and p-values will be tabulated. This analysis will be performed using the observed values without imputation of missing values.

13.2.2 Pain response to treatment (recorded on tablet computer)

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

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

of other data that is collected but due to similar analyses described together with secondary endpoint evaluations at Week 12 and Week 26.

The percentage decrease from baseline in average pain intensity, recorded on the tablet computer, will be derived per subject as

$$\%\text{pain decrease} = \frac{\text{Baseline Pain Intensity - average pain intensity Week } x}{\text{Baseline Pain Intensity}} \times 100$$

with x being Week 12, Week 26, and Week 52 respectively.

The responder rate for a given percentage threshold is defined as the proportion of subjects with a % pain decrease equal to or above the percentage threshold, i.e. the 30% responder rate (30% responder) is the percentage of subjects with at least 30% pain decrease. The distribution (by changing the percentage threshold) of responder rates in a given week will be determined for each treatment group using percentage thresholds of 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100. Descriptive statistics will be displayed for those percentage thresholds as well as for non-responders.

In addition, 30% responders and 30% non-responders (subject who show a worsening or for whom the pain intensity score is missing and subjects with pain decrease <30%) will be displayed for Week 12, Week 26, and Week 52.

A graphical presentation for Week 12, Week 26 and Week 52 of the proportion of subjects defined as responders by treatment (y-axis) versus the threshold value (continuous scale) used to define a response (x-axis) will be produced. The 30% reduction as well as the 50% reduction will be indicated by vertical lines.

13.2.3 Dynamic mechanical allodynia

For a detailed description of the dynamic mechanical allodynia assessment please see protocol Section 12.3.2. Allodynia is rated on an 11-point NRS and assessed 5 times. A value of "10" corresponds to the individual maximum pain imaginable. The degree of pain sensitivity is calculated by the geometrical mean of the five pain ratings given (Maier et al. 2010).

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

In addition, descriptive summaries will be generated for the degree of pain sensitivity and displayed together with the respective changes from baseline.

13.2.4 Pressure pain threshold

For a detailed description of the pressure pain threshold please see protocol Section 12.3.2. Pressure pain threshold will be measured at both the affected and unaffected limb for all subjects. Measurements are repeated in 3 series of slowly increasing stimulus intensities and the respective pressure pain threshold is documented. For the final PPT, the arithmetic mean of all 3 consecutive measurements is calculated (Rolke et al. 2010, Mainka et al. 2014).

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

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

In addition, descriptive summaries will be generated for the ratio of the thresholds as well as for the changes from baseline.

13.2.5 Edema

For a detailed description of the Edema measurement, please see protocol Section 12.3.4. Edema will be measured at both the affected and unaffected limb for all subjects having edema as a positive CRPS sign at baseline (based on clinical judgment; sign "Asymmetric edema" ticked "yes" on the CRPS Severity Score at Visit 2). Each measurement of the limbs will be performed 3 times. The average of the 3 measurements will be used for further analysis.

The ratio of the averages of the affected and the unaffected (denominator) limb will be calculated.

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

In addition, descriptive summaries including changes from baseline will be generated for the averages of the affected and the unaffected limb and the ratio of the two averages.

13.2.6 Confirmatory testing strategy for secondary endpoints

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

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

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

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

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

13.3 Other efficacy data

To assess the efficacy of neridronic acid in subjects with CRPS other data is collected as described in Section 1.2 of the protocol and will be analyzed as described in the following chapters. Descriptive summaries will be generated for all visits where data is assessed as per schedule of events in Section 1.7 of the protocol. Analysis will be presented per visit and treatment if not specified differently.

13.3.1 Pain Intensity recording on the tablet computer

Analysis will be performed by descriptively summarizing average, worst and current pain intensity recorded on the tablet computer by visit and treatment group. In addition, changes from baseline and changes from Week 26 will be displayed. The value at Visit 2 is considered as baseline value.

Graphical display of the worst and current pain recording by visit and treatment will be done in addition to the primary endpoint graphical display of the average pain intensity recordings.

In addition, analysis will be repeated for subgroups defined by subjects who are treated in Treatment Period B in combination with the responder definition based on duration of response as defined in Section 13.3.2.

13.3.2 Pain response based on pain intensity recordings on the tablet computer

Pain response to treatment based on pain intensity recordings on the tablet computer will be analyzed based on the comparison timepoint, either baseline or Week 26.

Pain response as % decrease from baseline

Analyses are covered as part of secondary endpoint “Pain response to treatment” (see Section 13.2.2). In addition to the 30% responders and 30% non-responders a display with regards to the percentage threshold of 50% will be done. A 50% responder is a subject showing at least 50% pain decrease and a 50% non-responder being a subject with a missing pain intensity or a subject having less than 50% pain decrease.

Pain response as % decrease from Week 26

Descriptive statistics will be displayed for % decrease from Week 26 analogously to analysis of pain response as % decrease from baseline. This will be done using the pain intensity at Week 26 instead of baseline pain intensity for determination of the % decrease.

Duration of effect – Response based on duration of effect

The duration of effect for treatment period A is defined as the time from baseline to first loss of response. Response is defined as at least 30% decrease from baseline and first loss of response is the first time after achieving response that a subject shows less than 10% decrease from baseline. Duration of effect is then the time from baseline till the last timepoint before first loss of response. Pain assessments (tablet computer) that are considered for this analysis are those at Day 1 (Baseline), Week 6, Week 12, Week 16, Week 22 and Week 26.

Subjects never reaching a 30% decrease from baseline will have a duration of effect of 0 weeks. Subjects reaching a 30% decrease from baseline but showing no loss of effect, i.e. not dropping to below 10% decrease from baseline afterwards, will be censored at Week 26 with a duration of effect of 26 weeks. Else the duration of effect is taken as the last assessment a subject shows an effect (at least 30% response) before first experiencing a loss of response. e.g., if subject shows less than 30% decrease at Week 6, at least 30% decrease at Weeks 12 and 16 and at Week 22 less than 10% decrease, the duration of effect is set to 16 weeks.

Duration of effect will be analyzed using survival analyses with timepoints respective to the visits where pain is assessed on the tablet computer. A frequency table for the duration of effect will be provided for Follow-Up Period 1.

Furthermore, to assess the effect of a second treatment cycle, for those subjects who received two treatment cycles of neridronic acid, descriptive statistics for the change in average pain intensity from baseline, the change in average pain intensity from Week 26 and pain response as % decrease from baseline and from week 26 will be displayed for Follow-up Period 2 for the following responder subgroups based on duration of effect.

- Never-responders: subjects with a duration of effect = 0 weeks.
- Lost-responders: Subjects with a duration of effect <26 weeks.
- Responders: subjects with a duration of effect =26 weeks.

13.3.3 Pain intensity recording in the electronic diary

Analysis and display of average pain recorded in the electronic diary is described in Section 13.1.1). Derivation and analysis of worst and current pain intensities recorded in the electronic diary will be done in the same manner.

13.3.4 Active range of motion (AROM)

For a detailed description of the AROM please see protocol Section 12.3.5.

For subjects having decreased AROM at baseline (diagnosed based on clinical judgment; sign “Motor abnormalities” ticked “yes”, sub-category “decreased AROM” ticked “yes” on the CRPS Severity Score at baseline), both affected and unaffected limbs will be measured.

The AROM in each of the unaffected and affected limbs will be measured 2 times, the AROM consists of two components flexion and extension, the sum of both builds the AROM. The results of both measurements and both components will be documented; only the best performance of the 2 repetitions will be used for further analysis, i.e. the highest flexion and the highest extension value per limb will be added and used further.

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

Descriptive summaries including changes from baseline will be generated for the AROM of the affected and the unaffected limb and the ratio of the two. The summaries will distinguish between the CRPS locations and display results for upper extremity and lower extremity as well as left and right body site separately.

13.3.5 CRPS Severity Score

The signs and symptoms of CRPS are recorded using tablet computers. The investigator examines the signs. The subject reports his/her symptoms with a recall period of 48 hours. At the Enrollment Visit, patients record their symptoms with recall period since onset of CRPS.

To derive the CRPS severity score, the symptoms reported with recall period 48 hours will be used.

Subjects will be queried on 8 self-reported symptoms (queried YES or NO):

1. continuing, disproportionate pain;
2. allodynia and/or hyperalgesia;
3. temperature asymmetry;
4. skin color asymmetry;
5. sweating asymmetry;
6. edema;
7. dystrophic changes;
8. motor abnormalities.

Moreover, subjects will be examined for 8 signs (observed on examination, queried YES or NO):

1. hyperalgesia to pinprick;
2. allodynia;
3. temperature asymmetry by palpation;
4. skin color asymmetry;
5. asymmetric edema;
6. sweating asymmetry;
7. dystrophic changes; and
8. motor abnormalities.

Each sign or symptom is assigned a dichotomous value (1 = presence; 0 = absence). The resulting CRPS severity score ranges from 0 to 16, with higher scores indicating greater CRPS severity. If one of the 16 signs and symptoms is missing the CRPS severity score will not be calculated and is considered missing.

A descriptive summary will be created by sign/symptom and visit (recall period 48 hours),

A graphical display over the entire trial will be created for the proportion of subjects with a sign/symptom, for each of the signs and symptoms, all treatments will be presented in one plot.

Furthermore, a descriptive summary of the continuous CRPS severity score and the corresponding change from baseline will be generated. A graphical plot of the means and 95% CI of the CRPS severity score over time will be created. All treatments will be presented in one plot. Assessments at visit 2 are considered baseline assessments.

13.3.6 Patient Global Impression of Change (PGIC)

The observed values of the PGIC will be summarized descriptively (categorical). Furthermore, the following categories will be pooled and presented:

- 'very much improved' and 'much improved'
- 'much worse' and 'very much worse'
- 'very much improved' and 'much improved' and 'minimally improved'.
- 'no change' and 'minimally worse' and 'much worse' and 'very much worse'

13.3.7 Patient Global Impression of Severity (PGI-S)

The observed values of the PGI-S will be summarized descriptively (categorical) and shift tables with regards to the baseline assessment will be generated. In addition, a shift table between Week 52 and Week 26 will be produced.

13.3.8 EuroQoL-5 Dimension-5 level (EQ-5D-5L)

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.

The health state of the subject is coded by the vector of the reported levels in each of the 5 dimensions. An EQ-5D-5L Health Status Index will be derived from the 5-dimensional health status vector using a lookup table that can be downloaded from the website of the EuroQol group. The index set provided for the US in the spread sheet "EQ-5D-5L value sets" of the Excel file "EQ-5D-5L_Crosswalk_Value_Sets.xls" will be used to assign an index value to the health status vector of a subject. For the US general population, the possible EQ-5D-5L index scores range from -0.109 for the health status vector "*55555*" to 1.0 for the vector "*11111*" on a scale where an index value of 0.0 represents death and 1.0 represents perfect health.

The EQ-VAS ranges from 0 (worst imaginable health) to 100 (best imaginable health).

A descriptive summary of the 5 categorical EQ-5D-5L dimensions will be generated by dimension, and visit. Furthermore, a descriptive summary of the continuous EQ-5D-5L index and the EQ VAS, and the corresponding changes from baseline will be generated by visit. In addition, for Week 52 the change to Week 26 will be generated.

13.3.9 PROMIS-29 profile and PROMIS-EDDEP39

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

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

The following description can be found in the PROMIS – Adult Profile Instruments (2015).

Each question has five response options ranging in value from 1 to 5, except for the Pain Intensity item (Question number 29 [GLOBAL07]) which has eleven response options ranging in value from

0 to 10. A raw score is created from each domain that makes up the Profile. To find the total raw score for a domain with all questions answered, the values of the response to each question within the domain is summed up. For example, for the 29-item Profile, the lowest possible raw score within Anxiety is 4 (a score of 1 on all four items); the highest possible raw score is 20 (see all short form scoring tables in Appendix).

Descriptive summaries including changes from baseline for the domains will be generated. Question number 29 (GLOBAL07) will be descriptively summarized and changes from baseline will be calculated for Week 16 and Week 22 only

The Question EDDEP39 of the PROMIS Item Bank version 1.0 – Emotional Distress – Depression (PROMIS-EDDEP39) will be descriptively summarized. A shift table will be generated to display changes from baseline.

13.3.10 Short-Form McGill Pain Questionnaire 2 (SF-MPQ-2) - 6 neuropathic items

The SF-MPQ-2 is a single measure of the major symptoms of both neuropathic and non-neuropathic pain. The pain qualities will be assessed using the 6 neuropathic items from the SF-MPQ-2. A total score for the neuropathic subscale will be calculated as a mean of all 6 neuropathic items (Gauthier et al. 2014).

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

Descriptive summaries including changes from baseline will be generated for the neuropathic total score as well as for each of the 6 individual items.

13.3.11 Pain Catastrophizing Scale (PCS)

The PCS will be used as a measurement tool to capture pain catastrophizing; the scale will be completed by the subjects using the tablet computers.

Derivation and details on the analysis of the PCS is described in detail in the User Manual of the PCS (Sullivan et al. 2009). The PCS is a 13-item instrument asking subjects to indicate the degree to which they experienced each of 13 thoughts or feelings when experiencing pain, on 5-point scales with the end points (0) not at all and (4) all the time. The PCS yields a total score. The PCS total score is computed by summing responses to all 13 items and ranges from 0 – 52.

Descriptive summaries including changes from baseline will be generated for the total score.

13.3.12 Pain Self Efficacy Questionnaire (PSEQ)

Ten items were selected to reflect a wide variety of classes of activities and tasks. Respondents consider how confident they are performing each activity, while taking their pain into account. Each activity is rated by selecting a number on a 7-point scale, where 0 equals ‘‘not at all confident’’ and 6 equals ‘‘completely confident’’. A total score is calculated by summing the scores for each of the 10 activities, yielding a maximum possible score of 60. Higher scores reflect stronger self-efficacy beliefs (Nicholas 2007). The Total Score will be displayed by descriptive summaries including changes from baseline.

13.4 Health economic and work productivity data

13.4.1 Work Productivity and Activity Impairment Questionnaire: CRPS (WPAI: CRPS) (US sites only)

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.

Descriptive summaries will be generated for all questions and displayed by treatment and week.

13.4.2 Medical resources utilization (US sites only)

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.

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

Descriptive summaries will be generated by treatment and visit.

Parameters summarized are:

- Healthcare Utilization domain (No, Yes):
  - Hospitalization during past 12 weeks (if yes, number of times).
  - Emergency room treatment (no hospitalization) (if yes, number of times).
  - Nursing Home Stay (if yes, number of nights).
  - Health Care providers (multiple answers possible) (if yes, number of visits and number of phone calls).
- Home Service, Home Help, Formal and Information Caregiving, Devices
  - Home Services and Help (multiple answers possible) (if yes, number of times and average duration (min))
    - Cleaning services.
    - Meals delivered.
    - Formal childcare assistance.
    - Transportation.
    - Caregiving.
  - Special Product/Device/Tool
    - Special equipment/assistive tools.

14 ANALYSIS OF PHARMACOGENETIC DATA, OMICS DATA AND PHARMACODYNAMIC PARAMETERS

All measurements and analyses of pharmacogenetics data and omics data will be described in separate analysis plans.

14.1 Bone turnover markers and markers for disease severity or CRPS progression

Bone turnover markers will be analyzed in the PDS. Soluble interleukin-2 receptor (sIL-2R) will be analyzed in the SAF.

The following bone turnover markers are assessed:

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

All bone turnover marker data will be listed in a subject data listing.

Bone turnover marker values as well as sIL-2R values, including changes from baseline, will be descriptively summarized by parameter and time point. Baseline is defined by the value on Day 1 (Visit 2).

For bone turnover markers as well as sIL-2R values a graphical plot of the mean and 95% CI of bone turnover marker values over time will be presented. Similarly, a plot of the mean change from baseline of bone turnover marker values over time will be presented. Furthermore, a display by fasting and non-fasting status will be done as assessed on the 'Date of confirmed Visit' in the eCRF. The non-fasting status consists out of non-fasting, insufficient fasting and unknown categories.

All bone turnover marker data and sIL-2R data will be listed in a subject data listing.

15 SAFETY ANALYSES

No statistical tests for comparison of safety data between treatment groups will be performed.

Safety data will be summarized descriptively by treatment group and by visit if applicable.

All safety data will be presented for the SAF unless otherwise specified.

The interim integrated clinical trial report will report all safety data until the cut-off date (last subject performing its Visit 11 (Week 26)), regardless of whether data is assessed before or after Visit 11.

15.1 Adverse events

A treatment emergent adverse event (TEAE) is defined as any adverse event that based on start date and start time information occurs in the on-treatment-period as defined in Section 8.2.2.

A pre-treatment non-TEAE is an adverse event starting in the pre-treatment period as defined in Section 8.2.2.

If there are partial dates or times, an adverse event will be considered treatment emergent unless the information available will clearly exclude it. Further details can be found in Section 19.1.6.1.

Assignment of TEAEs to treatment will be based on the definition of the on-treatment-period given in Section 8.2.2, thus, TEAEs occurring during the on-treatment period are assigned to the respective treatment. TEAEs will be assigned to treatment based on their start date.

Display by trial phase refers to a display by:

- Treatment Period A/Follow-up Period 1.
- Treatment Period B/Follow-up Period 2.

For display by trial phase TEAEs starting in the Follow-Up Period 2 will be displayed within one of the four treatment groups according to their treatment schedule in Treatment Period A and B. Display for Treatment Period B/Follow-up Period 2 will in addition to the four treatment groups include a neridronic acid overall group combining all subjects that have received a dose of neridronic acid.

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

The causal relationship of TEAEs to IMP is categorized as follows:

Category	Assessment by investigator
Related	certain probable/likely possible
Not related	unlikely not related
Unknown	unassessable/unclassifiable conditional/unclassified causal relationship is missing

An adverse event is considered to be “expected” if it is one where the nature or intensity is consistent with the information in the neridronic acid investigator’s brochure. Otherwise it is considered to be an “unexpected” adverse event.

15.1.1 Adverse event summaries

The following overview tables will be generated by treatment group and overall and by trial phases as defined above.

1. Summary of the number and percentage of subjects with at least 1
   - TEAE.
   - Serious TEAE.
   - Non-serious TEAE.
   - Unexpected TEAE.
   - Related TEAE.
   - Related serious TEAE.
   - TEAE leading to discontinuation from IMP.
   - TEAE leading to discontinuation from the trial.

- Death.

The percentage denominator will be the number of subjects.

2. Summary of the number and percentage of TEAEs for:
   - TEAEs.
   - Serious TEAEs.
   - Non-serious TEAEs.
   - Unexpected TEAEs.
   - Related TEAEs.
   - Related serious TEAEs.
   - TEAE leading to discontinuation from IMP.
   - TEAE leading to discontinuation from the trial.
   - Death.

   The percentage denominator will be the total number of TEAEs.

15.1.2 Incidence, incidence rates and number of events

The incidence of an adverse event is defined as the number of subjects with occurrence of this adverse event during the period of interest.

The incidence rate (crude incidence rate [CIR]) of an adverse event is defined as the number of subjects with occurrence of this adverse event during the period of interest divided by the total number of subjects N in the respective group (e.g., treatment group).

The incidence, incidence rate, the number of events, and the percentage of events will be summarized by PT (sorted by decreasing incidence rate in the neridronic acid treatment arm for:

- TEAEs.
- Serious TEAEs.
- Non-serious TEAEs.
- Related TEAEs.
- TEAEs associated with acute phase reactions.

Percentages will be calculated related to the total number of subjects/events presented in the respective table e.g., for the presentation of PTs for serious TEAEs percentages will be related to the number of subjects with serious TEAE/the total number of serious TEAEs, respectively.

Adverse events associated with acute phase reaction include the PT Acute Phase Reaction in all cases. They also include the PTs Arthralgia, Bone Pain, Chills, Fatigue, Headache, Influenza-Like Illness, Musculoskeletal Chest Pain, Musculoskeletal Pain, Myalgia, Pain, Pain In Extremity and Pyrexia, but only if occurring in the first 3 days after 1st IMP intake and not lasting longer than 3 days.

For serious TEAEs, percentages will additionally be presented related to the total number of all subjects/events, respectively.

The incidence, incidence rate, the number of events and the percentage of events will be summarized by SOC and PT (sorted alphabetically) for each:

- TEAEs.
- TEAEs with an incidence rate of at least 5% (≥ 5%) in any of the treatment groups.
- Serious TEAEs
  - Serious related TEAEs.
  - Serious fatal TEAEs.
  - Serious fatal related TEAEs.
- Non-serious TEAEs.
- Related TEAEs.

Percentages will be calculated related to the total number of subjects/events presented in the respective table e.g., for the presentation of SOC and PT for serious TEAEs percentages will be related to the number of subjects with serious TEAE/the total number of serious TEAEs, respectively.

For serious TEAEs, percentages will additionally be presented related to the total number of all subjects/events, respectively.

For all enrolled subjects, the incidence, incidence rate, the number of events and the percentage of events (related to the total number of events) will be summarized by SOC and PT (sorted alphabetically) for each:

- Pre-treatment non-TEAEs.
- Serious pre-treatment non-TEAEs.

Presentation will only be overall and not per treatment.

The number and percentage of events will be summarized by SOC and PT (sorted alphabetically) for the following TEAE descriptors:

- Intensity: mild, moderate, severe.
- Causal relationship to the IMP: related (with sub-categories: possible, probable/likely, certain), not related (with sub-categories: not related, unlikely), unknown (with sub-categories: conditional/unclassified, unassessable/unclassifiable, causal relationship missing).
- Outcome: recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal, unknown.
- Non-IMP related countermeasures: none, newly started medication, trial discontinuation, others.
- Action taken with IMP: drug interrupted, drug withdrawn, dose not changed, not applicable, unknown.

Denominator for percentage calculation will be the number of all TEAEs for presentation of overall SOCs, and the number of TEAEs per SOC or PT respectively, for the presentation per SOC or PT, respectively.

Measures of location and variation will be calculated for:

- Duration of TEAEs.
- Time to onset of TEAE (days).

In addition, the time to onset of TEAEs will be summarized using time-to-event methods for the overall 5 most frequent TEAEs. Time will be weeks, until onset.

The following listings will be produced for all enrolled subjects:

- Deaths.
- Serious adverse events other than death.
- Adverse events leading to discontinuation from the trial.
- Adverse events leading to discontinuation from IMP.
- Adverse events leading to IMP dose decrease or interruption of IMP.
- Adverse events associated with the acute phase reaction.

15.2 Laboratory parameters, vital signs and ECG parameters

This section defines the general principles for the analysis of categorical and continuous parameters, unless specified otherwise. In general, the analysis of all parameters will be done by visit and by treatment group.

Categorical parameters will be descriptively summarized per visit and overall post-baseline. For an overall post-baseline analysis, the worst value during the on-treatment period, including unscheduled visits, will be derived.

If applicable, the number of not exact values will be displayed in the respective table. Continuous parameters will be descriptively summarized. Changes from baseline will be presented for all post-baseline visits. Baseline values are defined as described in Section 8.2.2.

Where applicable, continuous parameters laboratory, vital signs, ECG parameter will be classified as *low*, *normal*, or *high* based on reference ranges and for parameters where sponsor alert ranges are defined as *alert low*, *non-alert*, or *alert high* (for laboratory parameters alert ranges are transferred with the data, for vital signs and ECG see Section 19.3). For an overall post-baseline analysis, values during the on-treatment period, including unscheduled visits, will be considered. If a subject has parameter values flagged as *low* and values flagged as *high*, the parameter will be classified as *low+high, alert low + alert high , respectively*.

A summary of the number and the percentage of subjects with values flagged as *alert low, non-alert, alert high* with respect to alert ranges will be provided for each continuous parameter.

Shift tables from baseline for the different visits and overall post-baseline will be generated for each continuous parameter flagged as *low*, *normal*, or *high* with respect to reference ranges. Denominator for the percentage calculation within each baseline category (*low*, *normal*, or *high*) will be the number of subjects at the respective visits.

Graphical presentations of the time course of specific continuous parameters and corresponding changes from baseline will be provided (mean and 95% confidence interval). At each visit, the plots will show the total number of subjects by treatment. On the bottom, the number of subjects flagged as *low*, and on the top the number of subjects flagged as *high* based on reference ranges (and *alert low* or *alert high* based on alert ranges), will be shown by treatment.

Shift plots by visit will be provided for specific continuous parameters with reference ranges and sponsor-defined alert ranges marked by vertical and horizontal lines}.

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

All parameter values will be presented in a subject data listing including respective flagging with respect to reference ranges and to sponsor-defined alert ranges.

Unscheduled measurements of parameters will be presented in the subject data listing. In general, unscheduled measurements will not be included in the analysis. However, they will be taken into account in the calculation of the overall post-baseline classification of parameters.

15.2.1 Laboratory parameters

Continuous and categorical laboratory parameters will be analyzed as described in Section 15.2 with individual specifications outlined in Table 2. The display of continuous laboratory parameters will be by parameter group (clinical chemistry, clotting, hematology, and urinalysis). Categorical urinalysis parameters will be additionally classified as normal or abnormal.

Central laboratory parameters will be analyzed as described in the following paragraphs. No statistical analysis of local laboratory assessments, pregnancy tests, and drugs of abuse tests will be done. In general, all central laboratory parameters will be reported using Système International d'Unités (SI) units. Selected parameters will additionally be reported using US conventional units to facilitate safety data review (Section 19.4). The corresponding analyses of these parameters will be repeated using values in US conventional units.

Subjects potentially qualifying for Hy´s law criteria (FDA 2009), i.e., subjects showing post-baseline abnormal hepatic values, will be presented in a separate listing. Subjects fulfilling the following 2 criteria potentially qualify for Hy's law:

- ALT > 3x ULN or AST >3x ULN.
- Total bilirubin > 2x ULN.

Table 2: Analysis of laboratory parameters

Parameter group	Parameter	Table of descriptive statistics	Frequency table (low/high)	Shift table	Mean plot	Shift plot
Clinical chemistry parameters (continuous)	Albumin	X	X	X		
	Alkaline phosphatase	X	X	X	X	X
	ALT	X	X	X		
	AST	X	X	X		
	Bilirubin	X	X	X		
	Calcium (albumin-corrected	X	X	X	X	X

Parameter group	Parameter	Table of descriptive statistics	Frequency table (low/high)	Shift table	Mean plot	Shift plot
	Creatine phosphokinase	X	X	X		
	Creatinine	X	X	X	X	X
	Estimated GFR	X	X	X		
	GGT	X	X	X		
	Glucose	X	X	X		
	LDH	X	X	X		
	Magnesium	X	X	X		
	Parathyroid hormone	X	X	X		
	Phosphate	X	X	X		
	Potassium	X	X	X		
	Protein	X	X	X		
	Sodium	X	X	X		
	Tricylglycerol lipase	X	X	X		
	Urea	X	X	X		
	Uric acid	X	X	X		
	Vitamin D	X	X	X		
Hematology parameters (continuous)	Hematocrit	X	X	X		
	Hemoglobin	X	X	X		
	Platelet count	X	X	X		
	RBC	X	X	X		
	WBC	X	X	X		
Urinalysis parameters (continuous)	pH	X	X	X		
	Albumin (microalbumin)	X	X	X		
	Creatinine	X	X	X		
	Urinary albumin/creatinine ratio (semi-quantitive dipstick)	X	X	X		
	Calculated urinary albumin/creatinine ratio (central laboratory)	X	X	X		
Urinalysis parameters (categorical)	Bilirubin	X		X		
	Blood	X		X		
	Glucose	X		X		

Parameter group	Parameter	Table of descriptive statistics	Frequency table (low/high)	Shift table	Mean plot	Shift plot
	Ketone	X		X		
	Leukocytes	X		X		
	Nitrite	X		X		
	Protein	X		X		
	Urobilinogen	X		X		

ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyltransferase; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular value; RBC = red blood cell; WBC = white blood cell.

Graphical presentations over time and respective shift plots will be done for the following continuous laboratory parameters:

- Alkaline phosphatase.
- Calcium (measured).
- Creatinine (serum).
- Estimated glomerular filtration rate (eGFR).
- Quantitative urinary albumin/creatinine (central laboratory value).

Urine samples potentially obtained from women of child-bearing potential will be tested locally using a urine ß-human chorionic gonadotropin (ß-HCG) pregnancy dipstick test. The results will be presented in a subject data listing.

Urine samples will be obtained from all subjects at the Enrollment Visit for testing for drugs of abuse. The drugs to be screened for using suitable validated methods (e.g., dipstick) include: cocaine, 3,4-methylendioxy methamphetamine, ecstasy (MDMA), amphetamines, cannabinoids. The results will be presented in a subject data listing.

15.2.2 Vital signs

Descriptive statistics for the vital signs parameters (systolic and diastolic blood pressure, pulse rate, weight, body mass index BMI [kg/m²]) will be analyzed as described in Section 15.2.

Frequency tables and shift tables with respect to sponsor-defined alert ranges as described in Section 15.2 will be created.

15.2.3 Electrocardiogram

Descriptive statistics for the electrocardiogram (ECG) parameters (continuous) heart rate, PR interval, QT interval, QTcF interval, RR interval will be analyzed as described in Section 15.2.

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

In addition, a subject data listing of all abnormal, clinically relevant findings as documented by the investigator in the e-CRF will be created.

15.3 Physical examination

A general physical examination will be done at the Enrollment Visit (Visit 1) by rating each body system as *normal* or *abnormal*. At all subsequent visits, including unscheduled visits, updates of the physical status since the previous visit are recorded by rating the body system as *unchanged* or *changed*.

The results will be presented in a subject data listing.

16 INTERIM ANALYSIS

16.1 Interim analysis of efficacy

The interim analysis will be further described in a separate SAP as it will be performed on the pooled data of two trials.

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18 CHANGES TO THE SAP

18.1 Amendments

Not applicable.

19 APPENDIX

19.1 Data derivation and analysis rules

The purpose of this section is to give technical details for the implementation of the SAP.

19.1.1 General specifications

19.1.1.1 Percentages and decimal places

If not otherwise specified, the following rules are applied:

- Percentages are presented to 1 decimal point.
- Percentages equal to 0 or 100 are presented as such without a decimal point.
- For descriptive summary statistics, the same number of decimal places as in the raw data are presented when reporting minimum and maximum values, 1 more decimal place when reporting mean, median, quartiles and confidence interval and standard deviation.
- P-values are presented to 3 decimal points. P-values <0.001 will be reported as such.
- Ratios are presented to 3 decimal points.

The above described displaying rules must not be changed (e.g., rounding) for the integrated clinical trial report text and are used 1:1 in the body report as well.

19.1.1.2 Presentation of descriptive statistics

Calculation of mean: if not otherwise specified, the arithmetic mean is used.

Table 3: Presentation of descriptive statistics in clinical trials

Number of non-missing values	n	Missing n	Mean	SD	Min	Q1	Median	Q3	Max
0	+	+	-	-	-	-	-	-	-
1.2.3.4	+	+	+	-	+	-	+	-	+
≥5	+	+	+	+	+	+	+	+	+

+ summary statistic will be presented; - summary statistic will not be presented.

CI = confidence interval, Max = maximum, Min = minimum, n = number of values, Q1 = first quartile, Q3 = third quartile, SD = standard deviation

19.1.1.3 Presentation of differences and changes

For differences between active comparator and placebo, the active comparator will constitute the minuend and placebo the subtrahend.

For changes from baseline, the baseline value will constitute the subtrahend and the later value the minuend.

19.1.1.4 Trial day count

The day of baseline visit (Visit 2) is defined as trial Day 1.

Calculate the trial day according to the following rules:

- If date < trial Day 1, then trial day = Date – trial Day 1.

- If date ≥ trial Day 1, then trial day = Date – trial Day 1 +1.

19.1.1.5 Presentation of units

If applicable, parameters will be displayed together with the used unit of measurement. The unit of measurement is enclosed in square brackets ([ ]).

19.1.1.6 Presentation of dates

Where applicable (e.g., in listings), dates will be displayed in ISO8601 format (example: 2014-09-29T12:16, see CDISC 2013). In case of incomplete dates, both the original value and the imputed value is displayed.

19.1.1.7 Handling of missing values

At each time point/visit, all subjects still in the trial are reported. This is defined as all subjects that have not discontinued the trial before the respective visit and are identified by a visit date. Missing values will be taken into account as missing in the analysis. The number of observed values and the number of missing values must add up to the number of subjects in the trial at the respective time point/visit.

Unless otherwise specified in the SAP, missing values will not be imputed. If missing values are imputed, the result of all imputation strategies and newly derived information must be stored in the ADaM data set. The shifts required for the shift tables should already be included in the ADaM data set.

Imputed values will be listed in the subject data listing and marked as imputed.

19.1.1.8 Visit windows

Since all assessments not done in the eDiary assessments are linked to specific visits no visit windows definition is needed are needed. Nevertheless if values or changes from baseline to a specific week are to be displayed the respective visit value is to be used. E.g. for responder analysis based on the tablet computer described in Section 13.2.2 the average pain intensity Week 26 is needed, which in fact related to the value documented for Visit 11.

19.1.1.9 Handling of data from early termination visits

Subjects who discontinue the 52-week trial period before their Week 52 visit (Visit 17) are requested to undergo an Early Termination Visit with identical procedures to Visit 17. Data from the Early Termination Visit recorded under Visit 17 will not be included in the analysis of data from scheduled visits at Visit 17.

Instead data from the Early Termination Visit will be assigned to the nearest scheduled visit based on the study day of the early termination visit and the planned visit day. The planned visit day is

- Day 1 for Visit 2
- Day 4 for Visit 3
- Day 7 for Visit 4
- Day 10 for Visit 5
- Day 15 for Visit 6
- Day 43 for Visit 7

- Day 85 for Visit 8
- Day 113 for Visit 9
- Day 155 for Visit 10
- Day 183 for Visit 11
- Day 186 for Visit 12 (only if subject is retreated)
- Day 189 for Visit 13 (only if subject is retreated)
- Day 192 for Visit 14 (only if subject is retreated)
- Day 197 for Visit 15 (only if subject is retreated)
- Day 253 for Visit 16
- Day 365 for Visit 17

In case of equal distance to two scheduled visits the earlier visit will be chosen. If the assigned visit already occurred before the early termination visit, then the data will be assigned to the next scheduled visit. Visits 12, 13, 14 and 15 are only applicable for subjects who have been treated in Treatment Period B.

Data from the Early Termination Visit will be analyzed using the re-assigned visits.

19.1.1.10 Assessments of on-treatment-period

For the calculation of the on-treatment-period the date information given for IMP administration will be used as documented in the e-CRF and according to the definition in Section 8.2.2.

19.1.1.11 Conversion of time intervals

If a time interval was calculated in minutes, hours or days and needs to be converted into months or years, the following conversion factors will be used:

- 1 month = 30 days.
- 1 year = 365.25 days.

19.1.1.12 End of treatment

End of treatment is the date of last administration of IMP given on the End-of-trial page in e-CRF.

19.1.1.13 Mandatory tables without data

Recommended tables must be created. If no subject qualifies for the table, the header will be created and the table itself will be replaced by “No subject in this category”.

19.1.1.14 Kaplan-Meier analysis

For Kaplan-Meier analyses in the 12-week trial period, the unit of time is days, the start time is the date/time of first IMP, and the censoring time is the day of Visit 8 or, in case of dropouts, the day of the Early discontinuation Visit 17.

19.1.2 Disposition

There are no trial-specific definitions for this trial.

19.1.2.1 Subject discontinuation

Reasons for subject discontinuation as specified in the End-of-trial page or reason for permanent discontinuation of IMP from the respective Treatment Period A/B completer page of the e-CRF will be used.

19.1.2.2 Protocol deviations

Protocol deviations are based on the analysis dataset ADDV. Major protocol deviations are retrieved from the respective SDTM dataset (SDTM.DV.DVCAT). No further protocol deviations are programmed in the analysis datasets for ADDV (if not otherwise specified in the SAP).

19.1.3 Demographics and other baseline characteristics

19.1.3.1 Subject demographics

Derivation of age

Age as derived in SDTM.DM.AGE will be used

Derivation of BMI:

BMI is extracted from the SDTM.

Derivation of race:

If for race more than 1 entry per subject is documented, a category “multiple” will be created.

19.1.3.2 CRPS history

For CRPS history, time since inciting or precipitating event (months), time since onset of CRPS symptoms (months), time since diagnosis of CRPS (months) are derived.

If the corresponding date reported in the eCRF is incomplete, e.g., missing day or month (year is mandatory), then the missing day or month will be imputed. Missing dates will be imputed conservatively, i.e., missing values will be imputed in such a way that the imputed date leads the longest possible time since event. Missing months will be imputed by the first calendar month of the year, and missing days will be imputed by the first calendar day of the (imputed) month.

Missing date	Imputed date
2018-Mar	2018-Mar-*01*
2018	2018-*Jan-01*

19.1.3.3 Prior and concomitant medication or therapy

Prior and concomitant medication is collected as of enrollment in the e-CRF and described like that in the trial protocol. For the analysis, the definition as described in the following is used.

The following rules are used to define the categories “prior” and “concomitant” medication.

Pre-requisite is a complete date of first dose of IMP (entered or imputed).

Stop of medication Date	Condition	Category
Complete date is available	Stop date is earlier than date of first dose of IMP.	Prior
Missing month	Year of stop date is earlier than year of first dose of IMP.	Prior
Missing day	Month/year of stop date are earlier than month/year of first dose of IMP.	Prior
Otherwise		Concomitant

Medication ticked in the e-CRF as "continuing" will be classified as concomitant.

For time to first concomitant analgesic medication start dates might need to be imputed. Imputation will be done as for CRPS history but if imputed date would be before first IMP date of first IMP will be used.

19.1.4 Efficacy analysis

Not applicable.

19.1.5 Analysis of pharmacokinetic and pharmacodynamic parameters

Not applicable.

19.1.6 Safety analysis

19.1.6.1 Adverse events

The result of all imputation strategies (e.g., incomplete start dates of adverse events), combination of observations and new derived information (e.g., treatment-emergent flag) must be stored in ADaM data set.

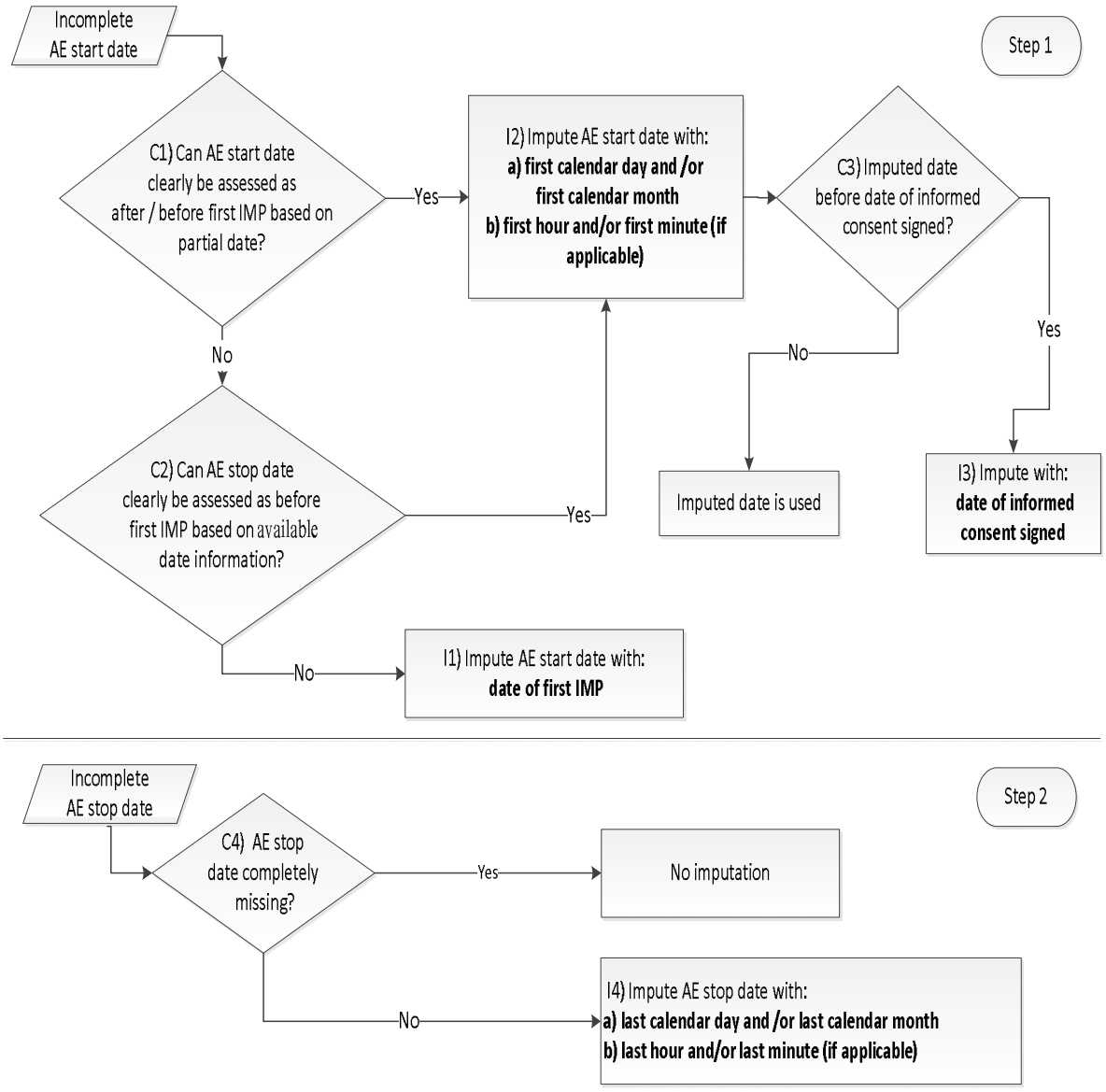
Handling of missing date information

The term missing date/time refers to a completely missing date /time or to an incomplete date/time where parts are not available e.g., missing hours.

The following imputation strategy is applied.

If the number of adverse events with missing date/time information exceeds 10%, the imputation strategy is only applied to assess if an adverse event is a TEAE but not for any other calculation (e.g., duration, onset).

Missing start and end date/times will be imputed conservatively, i.e., missing values will be imputed in such a way that the duration of the adverse event is considered with the longest possible duration and such that, whenever the adverse event may potentially start after first IMP administration, the adverse event will be handled as a TEAE.



I1-I4: imputation steps
C1-C4: checkpoints
AE = adverse event, IMP = investigational medicinal product

Figure 1: Graphical overview about the imputation strategy

Further explanations on the flow chart:

The different steps of the displayed imputation strategy must be completed from the first to the last step. All procedures in each step must be completed in the order given.

- Imputation:
  - I1: Impute with date/time of first IMP
    {If administration of IMP was not collected with time information set adverse event start time to 00:00.}
  - I2:
    a) Impute with first calendar day and/or first calendar month
    Imputation will be done based on the available partial information starting with month and then day. The respective first month and day will be chosen for imputation:

Missing date	**Imputed date**
2014-Mar	2014-Mar-*01*
2014	2014-*Jan-01*

b) Impute with first hour and/or first minute
Imputation will be done based on the available partial information starting with hour and then minutes. The respective first hour of a day and first minute will be chosen for imputation. “00:00” will be considered as the first hour/first minute per day.

Missing time	**Imputed time**
11:--	11:*00*
--:--	00:00

}

  - I3: Impute with date/time of informed consent signed
    If signing of informed consent was not collected with time information, set the adverse event start time to 00:00.

  - I4:
    a) Impute with last calendar day and/or calendar last month
    Imputation will be done based on the available partial information starting with month and then day. The respective last month and day will be chosen for imputation:

Missing date	**Imputed data**
2014-Mar	2014-Mar-*31*
2014	2014-*Dec-31*

For February leap years must to be taken into account when calculating the last day in February.

1.1. b: Impute with last hour and/or last minute
Imputation will be done based on the available partial information starting with hour and then minutes. The respective last hour of a day and last minute will be chosen for imputation. “23:59” will be considered as the last hour/last minute per day.

Missing time	Imputed time
11:--	11:59
--:--	*23:59*

- Checkpoints
  - C1: The decision must be taken based on the available information (date /time) before imputation.
  - C2: Adverse event stop date before first IMP

1.2. 1) The decision must be taken based on the available information (date/time) before imputation.

2) If the end date is completely missing (with or without the information that the adverse event was continuing), this will be considered as after first IMP.

3) If no IMP was given, this will be treated as adverse event stop date before the first IMP.

  - C3: The decision must be taken based on the available information (date/time) before imputation.
  - C4: The decision must be taken based on the available information (date/time) before imputation.

A replacement of missing year for adverse event start information is not foreseen. If needed, this will be considered on a case-by-case decision which must be documented together with the documentation of ADaM data sets.

Assessment of TEAEs

The assessment whether an adverse event is a TEAE will be done after replacement of missing date/time information.

Assignment adverse events to time periods/trial phases

Assignment of adverse events to time periods/trial phases will be done after replacement of missing date/time information.

List of deaths

Death will be identified by outcome of adverse event equals “fatal”.

Please also check all PTs for “death”.

Treatment emergent adverse events leading to discontinuation from IMP or leading to discontinuation from trial

Treatment emergent adverse events leading to discontinuation from IMP will be identified as treatment emergent adverse events with “Action taken with IMP” being “Drug withdrawn”.

Treatment emergent adverse events leading to discontinuation from trial will be identified as treatment emergent adverse events with “Countermeasure” being “Trial discontinuation”.

Time to onset of adverse events

Time to onset of adverse events will be calculated based on the first administration of IMP based on the imputed value for adverse event start date/time.

Duration of adverse events

Duration of adverse event will be calculated based on the imputed values for adverse event start date/time and stop date/time.

If the duration of the adverse event could not be calculated due to unknown date information, the following assessment to categories will be used:

- If the adverse event is marked as “continuing” in the {e-}CRF, the duration will be categorized as “continuing”.
- Otherwise, the duration category will be set to “missing”.

Subject experiencing a non-serious treatment emergent adverse event

All subjects who had at least 1 non-serious TEAE will be taken into account regardless of the experience of a serious TEAE.

19.1.6.2 Laboratory parameters, vital signs and ECG parameters

For categorical parameters, 2 types of tables are created:

1. Frequency tables display the pre-defined categories by time point/visit and overall post-baseline.
2. Shift tables display the shift from baseline at each time point/visit and overall.

Both types of tables show the number of subjects still in the trial (n) at the time point/visit and the number of missing values (nMiss) at the time point/visit. For the overall presentation, all post-baseline values on treatment are taken into account and nMiss is the number of subjects without any on-treatment post-baseline values.

For all ordinary levels of the categorical parameter including missing values, both the number and the corresponding percentage is displayed. If no missing values occur at any time point/visit, then the number of missing values can be omitted.

For descriptive statistics of continuous parameters, n is the number of subjects with recorded values and nMiss is the number of missing values at the respective time point/visit. The analysis of changes from baseline (e.g., baseline versus End of treatment) is based on subjects with non-missing values at both visits; for all other subjects, the change is missing.

Unscheduled visits

Unscheduled visits are time points not planned in the protocol.

In listings, unscheduled visits will be listed as recorded. All visits will be ordered chronologically including the dates of unscheduled visits.

Unscheduled visits will be incorporated in the overall post-baseline summary in tables. If the date is incomplete, but it can be determined whether values were measured in the on-treatment period, they will be incorporated in overall post-baseline summaries. Unscheduled visits will be excluded from the per time point/visit presentation.

Not exact values

Not exact laboratory values such as < x, > x will not be included in the analysis of continuous parameters. The frequency of occurrence of not exact values will be displayed in the respective table where applicable.

Handling of not exact values in a categorical analysis is described in the section below ("Values out of range").

Values out of range

For presentation of laboratory values as out of normal/sponsor-defined alert ranges, the flags as created by the laboratory are used.

In tables where parameters are classified as abnormal low, normal, abnormal high based on reference ranges and alert low, normal, alert high based on sponsor-defined alert ranges as defined in SDTM datasets or Section 19.3, the available pre-defined categories must be displayed in tables even if there are categories to which no subjects belong. Categories that are not applicable must be omitted (e.g., HDL abnormal high).

For the overall post-baseline summary (including all on-treatment post-BL time points/visits), subjects might have both low and high values. These subjects will be categorized in a new category "high and low" and excluded from the categories "high" and "low". The inclusion of this category in the frequency and shift tables is only required if there are any subjects falling into this category.

Ordering of parameters

Laboratory parameters, vital signs and ECG parameters will be ordered alphabetically within their parameter group (e.g., hematology, clinical chemistry, and urinalysis). Time points/visits will be sorted chronologically. If changes from baseline are displayed by time point/visit, all visits will be displayed first followed by all the changes from baseline.

19.2 List of statistical output documentation

The statistical output documentation will contain the original SAS-output for the analyses (incl. sensitivity analysis) of the primary and the secondary endpoint. No subject numbers are to be display, and hence subject number output will be suppressed.

19.3 Reference ranges and alert ranges

Vital signs and ECG parameters will be flagged as low or high based on reference ranges and sponsor-defined alert ranges, respectively. This section defines the reference and alert ranges for vital signs, and the alert ranges for ECG parameters. No reference ranges are defined for ECG parameters.

19.3.1 Reference ranges for vital signs

The reference ranges for vital signs are defined in Table 4.

Table 4: Reference ranges for vital signs parameters

Panel	Parameter	LLN	ULN
Vital signs	Blood pressure (diastolic)	< 50 mmHg	> 90 mmHg
	Blood pressure (systolic)	< 90 mmHg	> 140 mmHg
	Pulse rate	< 60 bpm	> 100 bpm
	Respiratory rate	< 10 breaths/min	> 20 breaths/min

bpm – beats per minute. mmHg – millimeter of mercury. LLN – lower limit of normal. ULN – upper limit of normal.

19.3.2 Sponsor-defined alert ranges for vital signs

The following table defines the sponsor-defined alert ranges for those vital signs parameters where lower or upper limits are specified.

Table 5: Sponsor-defined alert ranges for vital signs parameters

Panel	Parameter	Alert low	Alert high
Vital signs	Blood pressure (diastolic)	-	> 110 mmHg
	Blood pressure (systolic)	< 80 mmHg	> 180 mmHg
	Pulse rate	< 45 bpm	> 120 bpm

bpm – beats per minute. mmHg – millimeter of mercury.

19.3.3 Sponsor-defined alert ranges for ECG parameters

The following table defines the sponsor-defined alert ranges for those ECG parameters where lower or upper limits are specified.

Table 6: Sponsor-defined alert ranges for ECG parameters

Panel	Parameter	Alert low	Alert high
ECG	Heart rate	< 45 bpm	> 120 bpm
	PR interval	-	> 270 msec
	QT interval	-	> 500 msec
	QTcF interval	<300 msec	> 480 msec

bpm – beats per minute. msec – milliseconds.

19.4 Laboratory parameters reported in US conventional units

Selected laboratory parameters will additionally be reported using US conventional units. The following table lists the selected parameters.

Table 7: Laboratory parameters reported in US conventional units

Lab panel	Parameter
Clinical chemistry panel (continuous)	Albumin
	Blood urea nitrogen (BUN)
	Calcium (albumin-corrected)
	Calcium (measured)
	Cholesterol
	Creatinine (serum)
	Glucose
	Magnesium
	Parathyroid hormone [a]
	Phosphorus
	Total bilirubin
	Total protein
	Triglycerides
	Uric acid
	Vitamin D
Hematology panel (continuous)	Hematocrit
	Hemoglobin
Urinalysis panel (continuous)	Urinary ACR
	Urinary creatinine

a) Enrollment Visit only.
ACR = albumin creatinine ratio; LDH = lactic acid dehydrogenase; MCHC = mean cell hemoglobin concentration.