kf7013-03-sap

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
[redacted]	Functional Expert Approval	16-May-2018 11:06 GMT+0
[redacted]	Biostatistics Approval	16-May-2018 11:12 GMT+0
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STATISTICAL ANALYSIS PLAN

Trial number:	KF7013-03
Title of trial:	Open-label safety trial of intravenous neridronic acid in subjects with complex regional pain syndrome (CRPS)
EudraCT number:	2016-001164-11
Universal Trial Number:	U1111-1180-8099
Development phase:	Phase III
Investigational medicinal product:	Intravenous neridronic acid

Version	Date	DMS version number
Final Version	12 Dec 2016	1.0
Amendment 01	15 May 2018	2.0

This document was approved according to the sponsor's standard operating procedures.

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2 ABBREVIATIONS

Abbreviation	Explanation
ACR	Albumin creatinine ratio
ADaM	Analysis Data Model
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BAP	Bone alkaline phosphatase
ß-HCG	ß-human chorionic gonadotropin
BMI	Body mass index
BPI	Brief Pain Inventory
CES-D	Center for Epidemiological Studies Depression Scale
CI	Confidence interval
CIR	Crude incidence rate
CRPS	Complex regional pain syndrome
CTX	C-terminal telopeptide of type I collagen
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EQ VAS	EuroQol visual analog scale
EQ-5D-5L	EuroQol 5-dimension 5-level questionnaire
EU	European Union
FAS	Full Analysis Set
ICTR	Integrated clinical trial report
ID	Identification
IMP	Investigational medicinal product
IRT	Interactive response technology
LSmeans	Least square means
MDMA	3,4-methylendioxy methamphetamine, ecstasy
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed effects model for repeated measures
MNAR	Missing-not-at-random
MRI	Magnetic resonance imaging
N, n	Number of subjects
nMiss	Number of missing values
NRS	Numerical rating scale
PASS	Pain Anxiety Symptom Scale
PDI	Pain Disability Index

Abbreviation	Explanation
PD Set	Pharmacodynamic Set
PGIC	Patient Global Impression of Change
PPS	Per Protocol Set
PINP	Procollagen type I amino-terminal propeptide
PT	Preferred Term
Q1	First quartile
Q3	Third quartile
QTcB	Corrected QT interval (according to Bazett's formula)
QTcF	Corrected QT interval (according to Fridericia's formula)
SAF	Safety Set
SAP	Statistical analysis plan
SAS	Statistical analysis software®
SD	Standard deviation
SI	Système International d'Unités
SOC	System Organ Class
SDTM	Study Data Tabulation Model
TCS	Treatment Completers Set
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
USA	United States of America
VAS	Visual analog scale
WHO-DD	World Health Organization Drug Dictionary

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 KF7013-03 in accordance with the protocol version 5.0 dated 17 Nov 2017, and the eCRF DMS version 5.0 dated 28 Jul 2017. The analysis will be performed by a contract research organization in accordance with this SAP.

4 TRIAL OBJECTIVES

Primary objective:

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

Secondary objectives:

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

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, open-label, single-arm, Phase III safety trial of intravenous neridronic acid in subjects with CRPS.

There will be an enrollment period lasting up to 60 days, a treatment period consisting of 4 infusions over 10 days, and a follow-up period of approximately 50 weeks (Visit 6 [Week 2] through Visit 11 [Week 52]). The subjects are expected to be in the trial for approximately 60 weeks (14 months). See Figure 1 for a summary of the trial as a flow diagram. For details, refer to the schedule of events defined in the trial protocol.

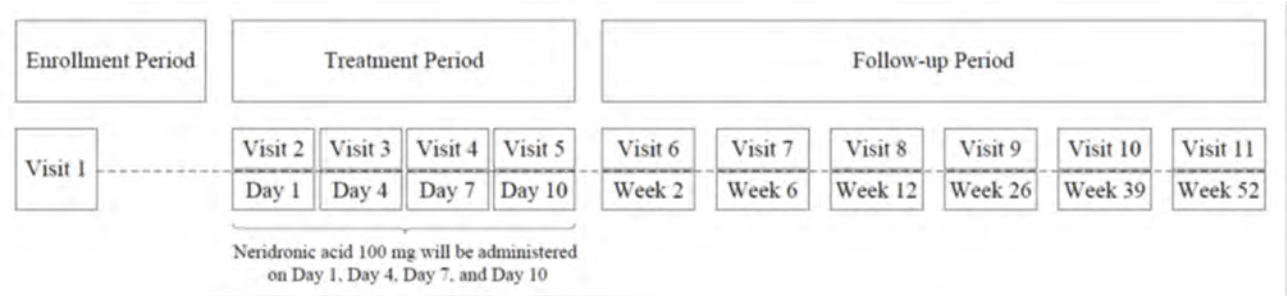

Figure 1: Flow diagram summary of the trial

The investigational medicinal product (IMP) is 100 mg neridronic acid diluted in 500 mL normal saline and administered by slow intravenous infusion (240 minutes [maximum 260 minutes]) at Visit 2, Visit 3, Visit 4, and Visit 5, resulting in a total dose of 400 mg neridronic acid.

In addition to the assessments applicable to all trial subjects, bone biopsies will be performed in a subset of trial subjects to assess the bone safety of neridronic acid 400 mg. In addition, bone imaging assessments (bone densitometry and magnetic resonance imaging) will be performed in a subset of trial subjects. Bone biopsies and bone imaging data will only be obtained from subjects participating at sites in the United States of America (USA).

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

5.2 Sample size

The sample size is intended to maximize available safety data to support product registration. In combination with subjects receiving active treatment in the ongoing placebo-controlled trial (KF7013-01) and further planned trials of neridronic acid, the number of subjects included in this trial is intended to support regulatory requirements for at least 500 subjects on neridronic acid evaluated for safety. It is estimated that approximately 290 subjects will be included in this trial.

For bone biopsies, results from 15 evaluable biopsy specimens are considered adequate to be able to identify qualitative bone abnormalities such as osteomalacia as well as quantitative indicators of impaired mineralization.

For bone densitometry and magnetic resonance imaging (MRI) assessments, results from 30 subjects are considered sufficient to demonstrate feasibility and support a rationale for the future use of these assessments in trials of neridronic acid in CRPS.

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

5.3 Randomization

Not applicable.

6 OVERVIEW OF PLANNED ANALYSES

6.1 Final analysis

The final analysis will be performed after all subjects have completed the trial, and the data has been hard locked. The results of the final analysis will be the basis for the integrated clinical trial report.

6.2 Interim analyses

An external DMC will periodically review safety information from the trial and monitor trial conduct and overall progress. For details on the interim analysis, please refer to Section 17.

7 DOCUMENT AND CHANGE HISTORY

7.1 Changes in analysis compared to the trial protocol

This section summarizes the changes in the analysis compared to the protocol.

Protocol	SAP
Section 1.5.2 Full Analysis Set: All subjects who are allocated and treated.	**Section 9.4** The Full Analysis Set includes all subjects allocated with at least 1 IMP administration, *including any partial infusion*. Reason: To align with the definition of the SAF.
Section 14.1.3 The Pharmacodynamic Set includes all subjects with at least 1 non-missing value for at least 1 of the bone turnover markers.	**Section 9.4** The Pharmacodynamic Set includes all *treated* subjects with at least 1 non-missing value for at least 1 of the bone turnover markers Reason: Only treated subjects were intended for inclusion in this analysis set.

7.2 Rationale for changes from pre-final to final SAP

Not applicable.

7.3 SAP amendment rationale

The rationale for amendment 01 on the final SAP is to implement the changes resulting from the protocol amendments and project decisions . In addition, minor corrections and revisions were performed.

In the table below, deleted text is crossed out and new text is highlighted using italics.

Change from final	Rationale for change
Section 3 This statistical analysis plan (SAP) includes all definitions and analysis details for the analysis for DMC periodic meetings of the trial KF7013-03 in accordance with the protocol version ~~4.0~~*5.0* dated ~~19 Apr~~ *17 Nov* 2017, and the eCRF version ~~1.0~~ *5.0* dated ~~17 Nov 2016~~ *28 Jul 2017*. The analysis will be performed by a contract research organization in accordance with this SAP.	Update to the latest version of protocol and eCRF.
Section 5.1 The sample size is intended to maximize available safety data to support product registration. In combination with subjects receiving active treatment in the ongoing placebo-controlled trial (KF7013-01) and further planned trials of neridronic acid, the number of subjects included in this trial is intended to support regulatory requirements for at least 500 subjects evaluated for safety. It is estimated that approximately ~~220~~ *290* subjects will be included in this trial~~; the actual number of subjects allocated, however, may depend on enrollment in ongoing and further planned trials~~.	According to Protocol Amendment 5, the sample size was increased.
Section 8.2.1 ~~Not applicable.~~ *Two subgroups will be defined based on the duration of CRPS:* *1. Subjects with duration ≤2 year from onset of symptoms suggestive of CRPS.* *2. Subjects with duration >2 year from onset of symptoms suggestive of CRPS.* *When subgroup analyses are specified, the analysis will be performed separately in each of the subgroups and overall.*	To add subgroup analyses.
Section 10.2 Reasons for discontinuations from the trial and from IMP will be presented for: • Subjects allocated and discontinued from the trial • Subjects allocated and discontinued IMP intake. • Subjects allocated and discontinued from the trial per trial phase, i.e., during the treatment period, and during the follow-up period ~~overall, and separately for the first 100 subjects (Visit 11) and for subsequent subjects (Visit 9)~~.	According to Protocol Amendment 1 from 21 Oct 2016, the design of the trial was changed, all subjects are treated and analyzed in the same way, no need for separate analyses.

Section 13.2 The following secondary efficacy endpoints will be analyzed *overall and by subgroups*: Change from baseline to Week 12 and Week 26 in the current pain intensity score, using a numerical rating scale (NRS). • Response to treatment, defined as at least 30%, ~~and~~ at least 50% *and at least 2 points on the NRS* decrease from baseline in the current pain intensity score, at Week 12 and Week 26. • Patient Global Impression of Change (PGIC) at Week 12 and Week 26. • Change from baseline to Week 12 and Week 26 in the Pain Interference score of the Brief Pain Inventory (BPI).	To add subgroup analysis for secondary efficacy endpoints and add '*at least 2 points on the NRS'* in the responder analyses
Section 13.2.1.2 Descriptive summaries of the responder status will be presented by visit for each of the 3 responder definition. This includes the summary of the secondary responder endpoints, i.e., the response to treatment defined as at least 30%, ~~and~~ at least 50% *and at least 2 points on the NRS* decrease from baseline at Week 12 (Visit 8) and Week 26 (Visit 9).	To add '*at least 2 points on the NRS'* in the responder analyses
Section 13.3 The following outcome parameters based on other efficacy data collected in this trial will be analyzed *for the FAS*:	To add analysis population for other efficacy data.
Section 15.2.1 In table 3, mean plot and shift plot are added for parathyroid hormone, vitamin D and calcium.	To align with the analyses for DMC
Section 20.1.1.14 *If the last available visit is between Visit 2 and Visit 7, data from the early termination visit will be assigned to the next scheduled visit; otherwise* ~~Visit 9 or Visit 11 in the follow-up period. D~~ data will be assigned to the nearest scheduled visit based on the trial day of the early termination visit and the planned visit day. The planned visit day is: • Day 182 for Visit 9 (Week 26). • *Day 273 for Visit 10 (Week 39).* • Day 365 for Visit 11 (Week 52).	To specify the imputation methods and programming instructions more clearly.
Section 19.2 ~~Not applicable.~~ Changes are made from Final SAP version 1.0 to SAP Amendment Version 2.0, all the changes are documented in Section 7.3.	To document the changes in the versions of SAP.

8 ANALYSIS CONVENTIONS

8.1 General principles

If 2 or more of the population sets as defined in the SAP coincide, presentations will only be prepared for 1 population.

All presentations will be done overall, i.e., for the single treatment group neridronic acid 400 mg.

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

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

- Continuous variables: 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 20.1.1.2.
- Categorical variables: absolute and relative frequencies. If not defined otherwise, the percentage denominator will be the number of subjects still in the trial at the respective time point in the analyzed population.
- Time-to-event variables: number of subjects, number of subjects with event, number of censored subjects, first quartile, median, and third quartile including 95% confidence interval. For calculating the survival estimate confidence interval (CI) bounds, the log-log transformed estimate of CI bounds will be used. In addition, Kaplan-Meier estimates and plots will be provided with the respective number at risk and the Kaplan-Meier estimates at the relevant time points together with the median and its 95% CI. Censoring mechanisms will be described in the respective section.

Medical terms (e.g., prior and concomitant diseases, adverse events) will be coded via Medical Dictionary for Regulatory Activities (MedDRA), and 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	TCS	PD Set
Subject disposition	X					
Discontinuations		X				
Protocol deviations			X			
Demographics			X			
Other baseline characteristics			X			
Subject medical history			X			
Previous and concomitant medication			X			
Exposure			X			
Compliance			X			
Primary safety endpoint			X			
Secondary safety endpoint			X			
Secondary efficacy endpoints				X	X	
Adverse events			X			
Laboratory values			X			
Vital signs			X			
Twelve-lead ECG			X			
Physical examination			X			
Bone turnover markers						X
Health economics data				X		

ECG = electrocardiogram; FAS = Full Analysis Set; PD Set = Pharmacodynamic Set; SAF = Safety Set; TCS = Treatment Completers Set.

8.2 Definitions

8.2.1 Definition of subgroups

Two subgroups will be defined based on the duration of CRPS:
1. Subjects with duration ≤2 year from onset of symptoms suggestive of CRPS.
2. Subjects with duration > year from onset of symptoms suggestive of CRPS.
When subgroup analyses are specified, the analysis will be performed separately in each of the subgroups and overall.

8.2.2 Further definitions

Term	Definition
Baseline	For this single-arm non-randomized trial, baseline is the last observation (scheduled or unscheduled) before first IMP administration, unless specified otherwise. In general, baseline is the value recorded at Visit 2. For physical examinations, a general assessment will be done at Visit 1, and at all subsequent visits (scheduled or unscheduled) the change compared to the previous visit will be assessed. For bone imaging assessments, a separate baseline visit must be scheduled during the enrollment period for subjects undergoing bone densitometry and magnetic resonance imaging procedures.
Early termination visit	Subjects who discontinue the follow-up period before their last planned visit should undergo an Early Termination Visit with procedures identical to Visit 11. If a subject discontinues then, the data recorded under Visit 11 in the eCRF are treated as data belonging to the Early Termination Visit.
Follow-up period	The follow-up period starts after the treatment period and ends at Visit 11.
Follow-up completers	Subjects completing Visit 11 in the follow-up period. Intermittent missed visits in the follow-up period are allowed and do not affect the follow-up completion status.
Investigational Medicinal Products (IMP)	Neridronic acid in the form of sodium neridronate hemi hydrate 108 mg for intravenous infusion (equivalent to 100 mg neridronic acid) supplied in 8 mL of excipients. The full contents of a single ampule or vial (8 mL) will be diluted in 500 mL normal saline and administered by slow intravenous infusion (240 minutes [maximum 260 minutes]) at Visit 2, Visit 3, Visit 4 and Visit 5, resulting in a total dose of neridronic acid 400 mg.
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 Visit 11 for trial completers, and otherwise at the Early Termination Visit for discontinued subjects. This is based on the persistence in bone and potentially prolonged effect of neridronic acid.
Pooling of sites	Individual sites will be combined to achieve pooled sites of similar size and with a sufficient number of subjects. Sites will be pooled by geographical region. The majority of sites are located in the United States of America (USA). Sites in the USA will be pooled in 4 regions based on United States (US) states: • US North East: Connecticut (CT), Delaware (DE), Illinois (IL), Indiana (IN), Maine (ME), Maryland (MD), Massachusetts (MA), Michigan (MI), New Hampshire (NH), New Jersey (NJ), New York (NY), Ohio (OH), Pennsylvania (PA), Rhode Island (RI), Vermont (VT), and Washington D.C. (DC). • US South East: Alabama (AL), Florida (FL), Georgia (GA), Kentucky (KY), North Carolina (NC), South Carolina (SC), Tennessee (TN), Virginia (VA), and West Virginia (WV). • US Midwest: Arkansas (AR), Colorado (CO), Iowa (IA), Kansas (KS), Louisiana (LA), Minnesota (MN), Mississippi (MS), Missouri (MO), Montana (MT), Nebraska (NE), New Mexico (NM), North Dakota (ND), Oklahoma (OK), South Dakota (SD), Texas (TX), Wisconsin (WI), and Wyoming (WY). • US West: Alaska (AK), Arizona (AZ), California (CA), Hawaii (HI), Idaho (ID), Nevada (NV), Oregon (OR), Utah (UT), and Washington (WA). The sites in Europe will be pooled in one region, European Union (EU).
Pre-treatment-period	Before first IMP administration (excluded), i.e., the period between signature of the informed consent form and first administration of IMP.

Term	Definition
Subjects discontinued from treatment	Subjects permanently discontinued from IMP, i.e., subjects who stopped treatment prior to, or at any time during Visit 2, 3, 4, or 5.
Treated subjects	Subjects with at least 1 administration of IMP, including partial infusions.
Treatment period	The treatment period includes the four infusion visits starting at Visit 2 up to Visit 5. If a subject is permanently discontinued from treatment, the treatment period ends at the visit of the last infusion.
Treatment completers	Treated subjects who completed IMP administration according to the protocol, i.e., subjects who received the full dose of all 4 planned infusions of IMP. Treatment completers form the Treatment Completers Set defined below.
Trial completers	All subjects completing Visit 11 according to the protocol.

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.

9.3 Safety Set

The Safety Set includes all subjects with at least 1 IMP administration, including any partial infusion. The Safety Set will be the primary analysis set in this trial.

Analysis on the SAF will be conducted on the actual treatment received.

9.4 Full Analysis Set

The Full Analysis Set includes all subjects allocated with at least 1 IMP administration, including any partial infusion. In this trial, the Full Analysis Set coincides with the Safety Set.

Analysis on the FAS will be conducted according to the allocated treatment. In this single-arm trial, the allocated treatment is the same as the actual treatment.

9.5 Treatment Completers Set

The Treatment Completers Set (TCS) includes all treated subjects who completed IMP administration according to the protocol, i.e., subjects who received the full dose of all 4 planned infusions of IMP.

9.6 Pharmacodynamic Set

The Pharmacodynamic Set (PD Set) includes all treated subjects with at least 1 non-missing value for at least 1 of the bone turnover markers will be included in the Pharmacodynamic Set.

9.7 Bone Biopsy Set

All subjects with at least 1 bone biopsy evaluable for histology or histomorphometry will be included in the Bone Biopsy Set.

9.8 Bone Imaging Set

All subjects with at least 1 DXA or MRI image evaluable for BMD (DXA) or bone marrow lesion volume (MRI) will be included in the Bone Imaging Set.

10 DISPOSITION

10.1 Subject disposition

All presentations for subject disposition will be overall, i.e., for the single treatment group neridronic acid 400 mg.

For describing the subject disposition, the following populations will be summarized:

- Subjects enrolled.
- Subjects enrolled but not allocated and reason for non-allocation.
- Subjects allocated.
- Safety Set.
- Full Analysis Set.
- Treatment Completers Set (i.e., Treatment completers).
- Pharmacodynamic Set.
- Bone Biopsy Set.
- Bone Imaging Set.
- Trial completers.
- Follow-up completers.
- Subjects allocated and discontinued from the trial.
- Subjects allocated and discontinued from the trial per trial phase, i.e., during the treatment period, and during the follow-up period.
- Subjects who received 4 infusions, including partial infusions.
- Subjects allocated and discontinued IMP intake.
- Subjects allocated and discontinued IMP intake due to deterioration in renal function.

For subjects enrolled but not allocated and for the reasons for not being allocated, the percentage denominator will be the number of enrolled subjects. For all other calculations, the percentage denominator will be the number of allocated subjects.

In addition, an overview table will be prepared presenting the number of subjects enrolled, allocated, in the SAF, in the FAS, in the TCS, PD Set, Bone Biopsy Set, and Bone Imaging Set if applicable per country. Percentage calculation will be done in two ways:

- The denominator will be the number of all allocated subjects.
- The denominator will be the number of allocated subjects in the respective country.

Reasons for exclusion from the analysis populations will be summarized. The percentage denominator will be the number of subjects allocated.

10.2 Subject discontinuations

Discontinuations from the trial and from IMP will be presented for allocated subjects overall, and per country.

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

- Subjects allocated and discontinued from the trial
- Subjects allocated and discontinued IMP intake.
- Subjects allocated and discontinued from the trial per trial phase, i.e., during the treatment period, and during the follow-up period

Percentage denominator will be the number of subjects discontinuing.

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

If more than 10% of the allocated subjects discontinue the trial/IMP the distribution of the time to discontinuation from trial/IMP will be summarized using time-to-event methods. Time will be days until discontinuation. The time to discontinuation from the trial will be censored at the subject's last planned visit, i.e., Visit 11. The time to discontinuation from IMP will be censored at the last planned infusion visit (Visit 5) or at the early termination visit in case of premature discontinuation from the trial, whichever occurs first.

All data will be presented in a subject data listing sorted by site.

10.3 Protocol deviations

Major protocol deviations will be summarized overall, and by pooled site and site based on the SAF and will be grouped into different categories such as:

Category code	Category definition
PD01	Violation of inclusion/ exclusion criteria
PD02	Time schedule deviations
PD03	Non-compliance regarding intake of IMP or rescue medication
PD04	Inappropriate intake of concomitant medication
PD05	Missing essential data
PD06	Subject not discontinued as per protocol
PD07	Other protocol deviations
NC08	Other GxP non-compliance

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

The list of definitions of protocol deviations (SDN-NONCOMP-DEF-01) may be updated during the trial and will be finalized before database lock. Multiple deviations can occur in the same subject and thus a subject can be counted in more than 1 deviation category.

11 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Subject demographics and baseline characteristics will be summarized descriptively overall, i.e., for the single treatment group neridronic acid 400 mg, for the SAF.

This also applies to the summaries of medical history including dental history and CRPS history, and the summaries of prior and concomitant medication or therapy.

11.1 Subject demographics

Subject demographics are age [years], height [m], sex, race, ethnicity, and age group. Age group will be derived. Age groups will be <18 years, ≥18 years and <65 years, ≥65 years and <85 years, and ≥85 years.

All demographic data will be presented in a subject data listing.

The continuous variables age and height will be descriptively summarized. Sex, race, ethnicity, and age group will be summarized as categorical variables.

Remark: Weight is recorded repeatedly together with the vital sign parameters. Therefore, weight and body mass index (BMI) are described in Section 15.2.2).

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 with assessments collected later on in the trial and not in a separate table. 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 electrocardiogram (ECG) parameters.
- Vital signs parameters.
- Bone turnover markers.
- Health economics questionnaires (WPAI-CRPS, medical resource utilization).

Moreover, the analysis of the urine drugs of abuse test at the Enrollment Visit is described in Section 15.2.1.

11.3 Subject medical history

11.3.1 Medical history

All medical history data will be presented in a subject data listing.

Medical history will be summarized and sorted alphabetically, separately for prior and concomitant diseases, by primary System Organ Class (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 analyzed separately in the same way as the medical history.

11.3.3 Complex regional pain syndrome history

All CRPS history data will be presented in a subject data listing.

The CRPS history will be descriptively summarized. Time since precipitating event, duration (time since onset of symptoms), and time since diagnosis will be calculated based on the date of Visit 1 and the corresponding CRPS-related dates reported in the eCRF, and will be summarized as continuous variables. Time will be displayed in years. The CRPS etiology (precipitating event), CRPS location, previous CRPS history, and imaging methods used to support prior diagnosis (or exclude other diagnoses) will be categorically summarized.

11.4 Prior and concomitant medication or therapy

Therapies will only be displayed in the subject data listings.

Prior and concomitant medication is collected in the eCRF 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. In addition, the number of subjects with medication started after last dose of IMP will be displayed.

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

12 EXPOSURE AND COMPLIANCE

Exposure and compliance will be analyzed overall, i.e., for the single treatment group neridronic acid 400 mg, for the SAF.

All exposure and compliance data will be presented in subject data listings.

12.1 Exposure

At each infusion visit (Visits 2, 3, 4, and 5), the full contents of an 8 mL ampule or vial will be transferred to an infusion bag containing 500 mL normal saline and administered by slow intravenous infusion.

The volume of IMP transferred to the infusion bag, the administered volume of the infusion, and the dose (amount of neridronic acid) and the cumulative dose will be listed by visit. For dose and cumulative dose, the actual and the planned dose will be displayed.

Actual dose and actual cumulative dose will be descriptively summarized by visit.

12.2 Compliance

At each infusion visit (Visits 2, 3, 4, and 5), compliance (%) will be calculated as the ratio of the dose actually administered, divided by the planned dose (100 mg). Moreover, the cumulative compliance will be derived at each infusion visit as the ratio of the actual cumulative dose divided by the planned cumulative dose. Compliance and cumulative compliance will be descriptively summarized by visit.

Cumulative compliance at Visit 5 will be classified based on the following 4 intervals 0 - 25%, >25 - 50%, >50 - 75%, and >75% - 100%, and a descriptive summary will be presented.

In addition, a categorical summary of infusion data in the eCRF (questions *"Was the IMP administered to the subject?"*, and *"Was dose completely administered?"*) will be created by visit.

13 EFFICACY ANALYSES

All efficacy data will be analyzed overall, i.e., for the single treatment group neridronic acid 400 mg, for the FAS, unless specified otherwise.

All efficacy data will be presented in subject data listings.

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

13.1 Primary endpoint

Not applicable. No primary efficacy endpoint is defined for this trial.

13.2 Secondary endpoints

All secondary efficacy endpoints will be analyzed for the FAS and additionally for the TCS.

The following secondary efficacy endpoints will be analyzed overall and by subgroups:

- Change from baseline to Week 12 and Week 26 in the current pain intensity score, using a numerical rating scale (NRS).
- Response to treatment, defined as at least 30%, at least 50% and at least 2 points on the NRS decrease from baseline in the current pain intensity score, at Week 12 and Week 26.
- Patient Global Impression of Change (PGIC) at Week 12 and Week 26.
- Change from baseline to Week 12 and Week 26 in the Pain Interference score of the Brief Pain Inventory (BPI).

Since this is a single-arm trial, no hypothesis testing of secondary efficacy endpoints between treatment arms is planned. All secondary efficacy endpoints will be analyzed descriptively.

13.2.1 Main analysis

This section defines the main analysis for the secondary efficacy endpoints.

13.2.1.1 Current pain intensity

Current pain intensities and the corresponding changes from baseline will be presented in a subject data listing. Baseline current pain intensities will be flagged in the listing. Current pain intensities including their changes from baseline will be descriptively summarized by visit.

The change from baseline values at all post-baseline visits from Visit 3 through Visit 11 will be analyzed using a mixed model for repeated measures (MMRM), including the covariate baseline pain intensity, and the factors pooled site and visit as fixed effects, and subject as random effect. An unstructured covariance matrix will be used to model the covariance structure. The degrees of freedom of the denominator will be estimated using the Kenward-Roger approximation (Kenward and Roger 1997).

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=9 is the total number of post-baseline visits, visits 3 to 11) 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.

Point estimates (LSmeans), standard errors, and 95% CIs for the factor visit in the MMRM model representing the change from baseline at each visit will be presented. A graphical plot of the model-based estimates and the 95% CI of the change from baseline of current pain intensity scores will be created.

13.2.1.2 Response to treatment

For each subject, the percentage change from baseline in current pain intensity will be calculated at each post-baseline visit (Visit 3 through Visit 11):

$$\%Change = \frac{Pain\ Intensity - \ Baseline}{Baseline} \cdot 100\%.$$

If the decrease is at least 30%, at least 50%, or at least 2 points on the NRS, the subject will be considered a responder for the respective threshold. If a subject shows a worsening or the pain intensity score is missing, the subject will not be considered a responder. This applies also to subjects with premature discontinuation where subsequent pain values are missing.

The percentage change from baseline, and the responder status (responder *Yes*/*No*) with respect to the 3 responder definitions will be presented in a subject data listing.

Descriptive summaries of the responder status will be presented by visit for each of the 3 responder definition. This includes the summary of the secondary responder endpoints, i.e., the response to treatment defined as at least 30%, at least 50% and at least 2 points on the NRS decrease from baseline at Week 12 (Visit 8) and Week 26 (Visit 9).

A graphical plot of the responder rates will be created by responder definition and visit.

For each of the 3 responder definitions, persistence of the treatment effect will be assessed by deriving a combined responder status for the following 3 time periods:

- Months 3 and 6 (Visit 8, and 9).
- Months 3, 6, and 9 (Visit 8, 9, and 10).
- Months 3, 6, 9, and 12 (Visit 8, 9, 10, and 11).

A subject is a combined responder if he/she is a responder at each of the visits mentioned in the definition of the respective time period. For the derivation of the combined responder status, the results of the individual visits are combined.

13.2.1.3 Patient Global Impression of Change

The PGIC will be assessed at Visit 7 through Visit 11. Subjects respond to the question "Since the start of the trial, my overall status is:" with 1 of 7 possible responses (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse). A response of "very much improved" or "much improved" is generally regarded as a clinically important outcome. The response to treatment based on the PGIC will be derived by classifying subjects with outcome "very much improved" or "much improved" as responders, and subjects with other outcomes as non-responders. Subjects with missing PGIC score will be considered as non-responders.

All PGIC scores and the derived responder status will be presented in a subject data listing.

A descriptive summary of the categorical PGIC scores and the responder status will be generated by visit. This includes the summary of the secondary PGIC endpoints at Week 12 and Week 26.

A graphical plot of the distribution of the PGIC will be created by visit.

13.2.1.4 Brief Pain Inventory

Subjects will complete the brief pain inventory (BPI) Interference Scale questionnaire at Visit 2 and Visit 7 through Visit 11.

The BPI is a multi-item scale measuring the impact of pain on functioning and well-being. The 7 pain interference items: general activity, walking, work, mood, enjoyment of life, relations with others, and sleep, are each rated on a 0 to 10 scale using a 24-hour recall period, with 0 indicating "does not interfere" and 10 indicating "completely interferes".

The total Pain Interference Score is calculated by adding the scores for the 7 questions and dividing by 7, i.e., the average of the 7 item scores. This gives an interference score with a range from 0 to 10. If not more than 3 of the 7 items are missing, the average is calculated based on the available 4, 5, or 6 item scores. If more than 3 of the 7 items are missing, the total score will not be calculated and is considered missing.

The scale can also be subdivided into activity (general activity, walking, work and sleep) and affective (mood, enjoyment of life, relations with others) subcomponents. For the activity and affective subcomponents, the subcomponent score will not be calculated and is considered missing if 1 of the item scores is missing.

All individual item BPI scores, the subcomponent scores, and the total score will be presented in a subject data listing.

A descriptive summary of the categorical individual item scores will be generated by item and visit. Furthermore, a descriptive summary of the continuous subcomponent scores and the continuous total score, and the corresponding changes from baseline will be generated by score type (subcomponent scores, and the total score) and visit. This includes the summary of the secondary BPI endpoints at Week 12 and Week 26.

13.2.2 Sensitivity analysis

Not applicable.

13.2.3 Other analysis

Not applicable.

13.3 Analysis of other efficacy data

The following outcome parameters based on other efficacy data collected in this trial will be analyzed for the FAS:

- Change from baseline to Week 12 and Week 26 in the worst pain intensity score, using an 11-point NRS.
- Change from baseline to Week 12 and Week 26 in the average pain intensity score, using an 11-point NRS.
- Change from baseline to Week 12 and Week 26 in the Pain Disability Index (PDI) score.
- Change from baseline to Week 12 and Week 26 in the EuroQoL-5 dimension 5 level (EQ-5D-5L) index score and the health-related visual analog scale (VAS) score.
- Change from baseline to Week 12 and Week 26 in the Pain Anxiety Symptom Scale (PASS) score.
- Change from baseline to Week 12 and Week 26 in the Center for Epidemiological Studies Depression Scale (CES-D) score.
- Change from baseline to Week 12 and Week 26 in the CRPS Severity Score.

13.3.1 Average and worst pain intensity

Worst and average pain intensities will be added to the subject data listing of current pain values (see Section 13.2.1.1). The listing will be presented by pain type (average, current, and worst).

Worst and average pain intensities will be added to the descriptive summary of current pain. The summary will be presented by pain type.

Change in the worst pain intensity and average pain intensity for all post-baseline visits will be analyzed using the same statistical model as the one used for the current pain.

Point estimates least square means (LSmeans), standard errors, and 95% CIs for the factor visit in the MMRM model representing the change from baseline at each visit will be presented. Results will be added to the model-based summary of current pain.

Graphical plots of the model-based estimates and the 95% CI of the change from baseline of worst and average pain intensity will be created. The plots will be added to the graphical plots of current pain intensity scores.

13.3.2 Pain Disability Index score

The PDI questionnaire will be completed by all subjects at Visit 2 and Visit 7 through Visit 11.

The PDI questionnaire includes questions related to pain-related disability in 7 categories: family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care, and life-support activities. For each of the 7 categories, the subjects are asked to rate on an 11-point NRS the level of disability they typically experience. The PDI is calculated as the sum of the 7 categories, for a minimum value of 0 and maximum value of 70. If one of the 7 items is missing the PDI score will not be calculated and is considered missing.

All individual PDI categories and the total score will be presented in a subject data listing.

A descriptive summary of the categorical individual category scores will be generated by visit. Furthermore, a descriptive summary of the continuous total score and the corresponding changes from baseline will be generated by visit. This includes the summary of the PDI score at Week 12 and Week 26.

13.3.3 EuroQoL-5 dimension 5 level score and VAS

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

The EQ-5D-5L has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the 5 dimensions has 5 possible levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

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).

All five EQ-5D-5L dimensions, the EQ-5D-5L index, and the EQ VAS will be presented in a subject data listing.

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. This includes the summary of the EQ-5D-5L index and the EQ VAS at Week 12 and Week 26.

13.3.4 Pain Anxiety Symptom Scale

The PASS questionnaire will be completed by all subjects at Visit 2 and Visit 7 through Visit 11.

The PASS questionnaire consists of 20 items designed to assess 4 aspects of pain-related anxiety: cognitive anxiety, escape-avoidance behaviors, fear of pain, and physiological symptoms of anxiety. Subjects rate each item in terms of frequency, from 0 (never) to 5 (always). The total score is calculated as the sum of ratings, with values ranging from 0 to 100; higher scores indicate higher levels of pain-related anxiety. If 1 of the 20 items is missing, the total score will not be calculated and is considered missing. A similar rule is applied to missing items in the calculation of the subcomponents. The subcomponents are defined in terms of the following item subsets (McCracken and Dhingra 2002):

- Cognitive anxiety: items 5, 10, 14, 17, and 19.
- Escape-avoidance behaviors: items 3, 6, 8, 11, and 20.
- Fear of pain: items 1, 2, 9, 13, and 16.
- Physiological symptoms of anxiety: items 4, 7, 12, 15, and 18.

All individual item PASS scores, the subcomponent scores, and the total score will be presented in a subject data listing.

A descriptive summary of the categorical individual item scores will be generated by visit. Furthermore, a descriptive summary of the 4 continuous subcomponent scores, the continuous total score, and the corresponding changes from baseline will be generated by visit. This includes the summary of the PASS total score at Week 12 and Week 26.

13.3.5 Center for Epidemiological Studies Depression Scale score

The CES-D questionnaire will be completed by all subjects at Visit 2 and Visit 7 through Visit 11.

The 20 items of the scale are symptoms associated with depression. Subjects are asked to rate each item from “rarely or none of the time (less than 1 day)” to “most or all of the time (5 to 7 days)” during the last week. Response scores for all questions except 4, 8, 12, and 16 are: <1 day = 0; 1-2 days = 1; 3-4 days = 2; 5-7 days = 3. For question 4, 8, 12, and 16, the scoring is reversed, i.e., <1 day = 3; 1-2 days = 2; 3-4 days = 1; 5-7 days = 0. The total CES-D score is calculated as the sum of scores for all 20 questions and has a range of 0 to 60. If of the 20 items is missing, the CES-D score will not be calculated and is considered missing.

All individual CES-D items and the total score will be presented in a subject data listing.

A descriptive summary of the categorical individual item scores will be generated by visit. Furthermore, a descriptive summary of the continuous total score and the corresponding changes from baseline will be generated by visit. This includes the summary of the CES-D total score at Week 12 and Week 26.

13.3.6 Complex Regional Pain Syndrome Severity Score

Signs and symptoms of CRPS will be assessed by the investigator at Visit 1 (enrollment), at Visit 2 (baseline) and Visit 7 through Visit 11 and recorded using the electronic patient reported outcome system.

The investigator examines the signs. The subjects are asked to report their symptoms with a recall period of 48 hours. At the Enrollment Visit, subjects are additionally asked to report their symptoms with a recall period since onset of disease for purposes of establishing the diagnosis of CRPS. This information is also used, in combination with the investigators assessment of signs of CRPS at

Visits 9, 10 and 11, to determine whether or not the subject continues to meet criteria for a diagnosis of CRPS at these latter visits (Table 2).

Table 2: Assessments of CRPS signs and symptoms

	Enrollment	Baseline	Post-baseline
	Visit 1	Visit 2	Visit 7 – Visit 11
Symptoms (recall period since onset) [a]	X		(X [c])
Symptoms (recall period 48 hours) [b]	X	X	X
Signs	X	X	X

a) Used for establishing the diagnosis of CRPS.

b) Used for CRPS severity score.

c) Values copied from Visit 1.

CRPS = complex regional pain syndrome.

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):

9. Hyperalgesia to pinprick.
10. Allodynia.
11. Temperature asymmetry by palpation.
12. Skin color asymmetry.
13. Asymmetric edema.
14. Sweating asymmetry.
15. Dystrophic changes.
16. Motor abnormalities.

Each sign or symptom is assigned a dichotomous value (1 = YES/presence; 0 = NO/absence). To derive the CRPS severity score, the symptoms reported with recall period 48 hours and the signs will be added. The resulting CRPS severity score ranges from 0 to 16. If the value for 1 of the

16 signs and symptoms is missing, the CRPS severity score will not be calculated and is considered missing.

The presence of CRPS at post-baseline Visits 7 to Visit 11 will be derived based on the "Budapest clinical diagnostic criteria" (Harden et al. 2010). For the Budapest criteria to be fulfilled, 3 criteria must be verified. The criteria are linked to the symptoms with recall period since onset and the signs in the following way:

1. Criterion (1): question 1 answered YES
2. Criterion (2): at least 3 of the following 4 symptom categories must be fulfilled:
   - Sensory: question 2 answered YES
   - Vasomotor: question 3 or question 4 answered YES
   - Sudomotor/edema: question 5 or question 6 answered YES
   - Motor/trophic: question 7 or question 8 answered YES
3. Criterion (3): at least 2 of the following 4 sign categories must be fulfilled
   - Sensory: question 9 or question 10 answered YES
   - Vasomotor: question 11 or question 12 answered YES
   - Sudomotor/edema: question 13 or question 14 answered YES
   - Motor/trophic: question 15 or question 16 answered YES

A subject data listing will present for:

- The individual signs and symptoms values (YES/NO).
- The answers to follow-up questions in case a sign or symptom is present.
- The CRPS severity score.
- The presence/absence of CRPS (Visits 7 through Visit 11).
- Comments.

A descriptive summary will be created by sign/symptom and visit for:

- The dichotomous symptoms and signs,.
- The dichotomous CRPS assessment (present/absent).

For the Enrollment Visit, symptoms with recall period since onset and symptoms with recall period 48 hours will both be summarized. A graphical display of the proportion of affected subjects over the entire 12-month trial period will be created including:

- The proportion of subjects with a sign/symptom, for each of the symptoms with recall period 48 hours and for each of the signs.
- The proportion of subjects meeting the diagnosis of CRPS, i.e., with CRPS presence.

Furthermore, a descriptive summary of the continuous CRPS severity score and the corresponding change from baseline will be generated by visit. A graphical plot of the means and 95% CI of the CRPS severity score over the entire 12-month trial period will be created.

14 ANALYSIS OF PHARMACOKINETIC AND PHARMACODYNAMICS PARAMETERS

In the following sections, a detailed description of all calculations and statistical methods used in the analysis of pharmacokinetic and pharmacodynamic parameters is presented.

Descriptive and graphical methods will be used to summarize the trial results.

Summaries will be grouped by treatment and time of assessment.

Missing data will be treated as such and will not be imputed or replaced in any way if not specified otherwise.

14.1 Analysis of pharmacokinetic data

Not applicable.

14.2 Analysis of pharmacodynamic data

Pharmacodynamic data comprise bone turnover markers and data from bone densitometry and MRI procedures. The analysis of pharmacodynamic data is described in the following sections.

14.2.1 Bone turnover markers

Bone turnover markers will be analyzed in the Pharmacodynamic Set.

The following bone turnover markers are assessed at Visit 2 and at Visits 6, 7, 8, 9, 10, and 11:

- 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, including changes from baseline, will be descriptively summarized by time point.

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.

14.2.2 Bone densitometry and magnetic resonance imaging procedures

Data collected in the electronic case report form (eCRF) will be listed for all subjects in the Bone Imaging Set. No further statistical analysis is planned in this SAP. Bone densitometry and MRI data will be analyzed and reported separately by a dedicated bone imaging service provider.

15 SAFETY ANALYSES

Safety data will be summarized descriptively overall, i.e., for the single treatment group neridronic acid 400 mg.

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

15.1 Adverse events

All adverse events with start date/time after first IMP administration in a subject administered a trial treatment will be defined as treatment emergent adverse events (TEAE) irrespective of causal relationship.

A pre-treatment non-TEAEs 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 20.1.6.1.

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

A TEAE is considered to be ‘expected’ when the nature or intensity is consistent with the information in the neridronic acid investigator’s brochure. Otherwise, it is considered to be an ‘unexpected’ TEAE. Expectedness will be assessed by the sponsor.

The following overview tables will be generated overall, i.e., for the single treatment group neridronic acid 400 mg.

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 TEAEs.
   - TEAE leading to discontinuation from IMP.
   - TEAE leading to discontinuation from the trial.
   - Deaths.

The percentage denominator will be the number of subjects.

2. Summary presenting the number of TEAEs per subject categorized as 0, 1, 2, 3, 4, 5, and >5.
3. Summary of the number and percentage of TEAEs for:
    - TEAEs.
    - Serious TEAEs.
    - Non-serious TEAEs.
    - Unexpected TEAE.
    - Related TEAEs.
    - Related serious TEAEs.
    - TEAE leading to discontinuation from IMP.
    - TEAE leading to discontinuation from the trial.

The percentage denominator will be the total number of TEAEs.

If more than 10 subjects discontinue the trial/IMP due to TEAE, the incidence and the incidence rate of TEAEs leading to discontinuation from the trial/from IMP will be summarized by SOC and PT.

If more than 5% of the subjects discontinue the trial due to TEAE, the distribution of the time to discontinuation from trial due to TEAE will be summarized using time-to-event methods. Time will be days until discontinuation. The time to discontinuation will be censored at the End-of-Trial Visit or at the time point of discontinuation if not due to TEAE.

If more than 5% of the subjects permanently discontinue IMP due to TEAE, the distribution of the time to discontinuation from IMP due to TEAE will be summarized using time-to-event methods. Time will be days until discontinuation. The time to discontinuation will be censored at the last planned infusion visit (Visit 5), or at the time point of discontinuation, whichever occurs first.

15.1.1 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 (CIR for crude incidence rate) 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 (related to the total number of events) will be summarized by PT sorted by decreasing incidence rate for:

- TEAEs.
- Serious TEAEs.
- Non-serious TEAEs.
- Related TEAEs.

A separate table per type of TEAE will be prepared. The tables will be restricted to events with an incidence rate of at least 5% (≥5%).

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:

- TEAEs.
- Serious TEAEs.
- Non-serious TEAEs.
- Related TEAEs.

For serious TEAEs, the incidence, the incidence rate, the number of events and the percentage of events will also be presented for serious related TEAEs, serious fatal TEAEs and serious fatal related TEAEs.

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. Presentation will be for TEAEs only.

- Intensity: mild, moderate, severe.
- Causal relationship to the IMP: related (with subcategories: possible, probable/likely, certain), not related (with subcategories: not related, unlikely), unknown (with subcategories: 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, not applicable, unknown.

Denominator for percentage calculation will be the number of all TEAEs for presentation 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.

In addition, the time to onset of TEAE will be summarized using time-to-event methods pooled over all TEAEs. Time will be days until onset. The time to onset will be censored at the End-of Trial-Visit, or at the time point of discontinuation if not due to TEAE.

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 permanent discontinuation from IMP.

In addition, adverse events associated with acute phase reaction will be presented for the SAF in a separate subject data listing. Adverse events associated with acute phase reaction include the PTs *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 first IMP intake and not lasting longer than 3 days.

For TEAEs associated with the acute phase reaction, the incidence, incidence rate, the number of events and the percentage of events (related to the total number of events) will be summarized by PT.

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, if applicable, by time point.

Categorical parameters will be descriptively summarized by presenting the number and percentage of subjects per visit/time point, and overall post-baseline. For an overall post-baseline analysis, the worst value during the on-treatment period, including unscheduled visits, will be derived.

Continuous parameters will be descriptively summarized. Change from baseline will be presented for all post-baseline visits/time points. Baseline values are defined as described in Section 8.2.2. If reference ranges for a parameter differ between subject groups, e.g., based on sex or age group, the analysis of the parameter will be presented separately for each subject group.

Continuous parameters will be classified as *low*, *normal*, or *high* based on reference ranges, and for parameters where sponsor alert ranges are defined, parameters will be classified as *alert low*, *non-alert*, or *alert high* based on sponsor-defined alert ranges. For an overall post-baseline analysis, the values out of range during the on-treatment period, including unscheduled visits, will be summarized per subject. If a subject has parameter values flagged as *low* and values flagged as *high*, the parameter will be classified as *low+high*.

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 where sponsor alert ranges are defined at each visit/time point and overall post-baseline.

Shift tables from baseline for the different visits /time points and overall post-baseline will be generated for each continuous parameter flagged as *low*, *normal*, or *high* with respect to reference ranges. Percentages will be calculated for each baseline category (*low*, *normal*, or *high*) using the number of subjects in the corresponding post-baseline categories.

Graphical presentations of the time course of continuous parameters and corresponding changes from baseline will be provided (mean and 95% confidence interval). At each visit/time point, the plots will show the total number of subjects. 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 sponsor-defined alert ranges will be shown by treatment.

Shift plots by visit/time point will be provided for the 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. For continuous parameters, values out of reference ranges will be flagged as H (high) or L (low) in the listing. If a value classified as high or low is in addition also out of sponsor-defined alert ranges, it will be flagged as H* or L* in the listing.

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

Central laboratory parameters will be analyzed as described in the following paragraphs. Local laboratory assessments, pregnancy tests, and drugs of abuse tests will only be listed.

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. The corresponding analyses of these parameters will be repeated using values in US conventional units. The list of parameters will be provided in a separate spreadsheet attached to the data management plan.

Continuous and categorical laboratory parameters will be analyzed as described in Section 15.2 with individual specifications outlined in Table 3. The analysis of continuous laboratory parameters will be done by parameter group (clinical chemistry, clotting, hematology, and urinalysis). Categorical urinalysis parameters will be additionally classified as *normal* or *abnormal*.

Graphical presentations of the mean time course of the continuous parameters alkaline phosphatase, calcium (measured), creatinine (serum), estimated glomerular filtration rate (eGFR), and calculated urinary albumin/creatinine will be provided (mean and 95% CI). The graph covers the 12-month trial period presenting the means from Visit 1 through Visit 11. Similarly, a graphical presentation of the mean time course of the change from baseline of the 5 parameters will be provided. The mean time course of each parameter and the corresponding change from baseline will be presented in 1 plot. The plots will be presented in US conventional units.

Shift plots by visit will be provided for the same parameters. The plots will be presented in US conventional units.

A graphical presentation of the mean time course of the laboratory parameters serum calcium (measured), urinary calcium and parathyroid hormone, and the bone turnover marker BAP (Section 14.2.1) will be created (mean and 95% CI). The 4 mean plots will presented as a single panel plot on the same page. The plot will be presented 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 3: 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		
	Bicarbonate	X	X	X		
	BUN	X	X	X		
	Calcium (measured)	X	X	X	X	X
	Calcium (albumin-corrected)	X	X	X		
	Chloride	X	X	X		
	Cholesterol	X	X	X		
	Creatine phosphokinase	X	X	X		
	Creatinine (serum)	X	X	X	X	X
	eGFR	X	X	X	X	X
	GGT	X	X	X		
	Glucose	X	X	X		
	LDH	X	X	X		
	Lipase	X	X	X		
	Magnesium	X	X	X		
	Parathyroid hormone	X	X	X	X	X
	Phosphorus	X	X	X		
	Potassium	X	X	X		
	Sodium	X	X	X		
	Total bilirubin	X	X	X		
	Total protein	X	X	X		
	Triglycerides	X	X	X		
	Uric acid	X	X	X		
	Vitamin D	X	X	X	X	X
Hematology parameters (continuous)	Hematocrit	X	X	X		
	Hemoglobin	X	X	X		
	MCH	X	X	X		
	MCHC	X	X	X		

Parameter group	Parameter	Table of descriptive statistics	Frequency table (low/high)	Shift table	Mean plot	Shift plot
	MCV	X	X	X		
	Platelet count	X	X	X		
	RBC count	X	X	X		
	WBC count [a]	X	X	X		
Urinalysis parameters (continuous)	Albumin (miroalbumin)	X	X	X		
	Calcium	X	X	X	X	X
	Creatinine	X	X	X		
	Calculated urinary albumin/creatinine ratio	X	X	X	X	X
	pH [b]	X	X	X		
Urinalysis parameters (categorical)	Bilirubin [b]	X		X		
	Blood (erythrocytes) [b]	X		X		
	Glucose [b]	X		X		
	Ketone [b]	X		X		
	Leukocyte esterase [b]	X		X		
	Nitrite [b]	X		X		
	Protein [b]	X		X		
	Urobilinogen [b]	X		X		

a) With differential count if abnormal: includes neutrophils, lymphocytes, monocytes, basophils, eosinophils (absolute count and percent).

b) Dipstick assessment.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; LDH = lactic acid dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean cell hemoglobin concentration; MCV = mean cell volume; RBC = red blood cell; WBC = white blood cell.

On Day 1, Day 4, Day 7, and Day 10, additional urine samples will be obtained prior to infusion for local laboratory assessment of urinary albumin creatinine ratio (ACR) at the site using a semi-quantitative dipstick. The results will be presented in a subject data listing.

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

Urine samples will be obtained from women of child-bearing potential (Visit 1 through Visit 5, Visit 9, and Visit 11) and 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

Vital signs comprise systolic and diastolic blood pressure, pulse rate, respiratory rate, body weight, and BMI. Vital signs will be measured at each visit (Visit 1 to Visit 11). At Visit 2 through Visit 5, vital signs will be taken once at least 15 minutes before the infusion and once at least 15 minutes after the infusion. Body weight will be included as a vital sign and will be measured at all visits (only once at Visit 2 through Visit 5, prior to the infusion). BMI will be derived.

Vital signs parameters will be analyzed as described in Section 15.2 with individual specifications outlined in Table 4.

Table 4: Analysis of vital signs parameters

	Parameter	Table of descriptive statistics	Frequency table (low/high)	Shift table	Mean plot	Shift plot
Vital signs parameters (continuous)	Blood pressure (diastolic)	X	X	X		
	Blood pressure (systolic)	X	X	X		
	BMI [a]	X	X	X		
	Body weight	X	X	X		
	Pulse rate	X	X	X		
	Respiratory rate	X	X	X		

a) BMI will be derived.
BMI = body mass index.

15.2.3 Electrocardiogram

Twelve-lead ECGs will be recorded from Visit 1 to Visit 6, at Visit 9, and at Visit 11. At Visit 2 through Visit 5, triplicate ECGs will be recorded once at least 15 minutes before the infusion and once at least 15 minutes after the infusion. One triplicate ECG will be recorded at all other visits.

Electrocardiogram parameters will include heart rate and the following ECG intervals: QRS, PR, RR, QT, QTcB, and QTcF. Twelve-lead ECGs are recorded in triplicate. For the analysis, the mean of the 3 individual values will be calculated for each parameter.

Electrocardiogram (ECG) parameters (continuous) will be analyzed as described in Section 15.2 with individual specifications outlined in Table 5.

Table 5: Analysis of ECG parameters

	Parameter	Table of descriptive statistics	Frequency table (low/high)	Shift table	Mean plot	Shift plot
ECG parameters (continuous)	Heart rate	X	X	X		
	PR interval	X	X	X		
	QRS interval	X	X	X		
	QT interval	X	X	X		
	QTcB interval	X	X	X		
	QTcF interval	X	X	X		
	RR interval	X	X	X		

ECG = electrocardiogram; QTcB = Corrected QT interval (according to Bazett's formula); QTcF = Corrected QT interval (according to Fridericia's formula).

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 eCRF will be created.

15.3 Physical examination

Physical examination outcomes will be recorded at Visit 1, before the IMP infusion at Visit 2, and from Visit 8 through Visit 11 in the follow-up period. 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 is recorded by rating each body system as *unchanged* or *changed*.

All physical examination results will be presented in a subject data listing.

15.4 Bone biopsy procedures

Data collected in the eCRF regarding bone biopsy procedures and tetracycline intake will be listed for all subjects in the Bone Biopsy Set. No further statistical analysis is planned in this SAP. Bone biopsy data will be analyzed and reported separately by a dedicated bone biopsy service provider.

15.5 Primary endpoint

The primary endpoint of this trial is a binary safety endpoint assessing whether or not a subject experienced any TEAE. The incidence and incidence rate for any TEAE is included in the summary of the number and percentage of subjects with TEAE (Section 15.1).

15.6 Secondary safety endpoint

The secondary safety endpoint is the occurrence of permanent discontinuation from treatment due to an adverse event. The number and percentage of subjects permanently discontinued from treatment is included in the summary of discontinuations from IMP (Section 10.2).

16 HEALTH ECONOMICS OUTCOME AND WORK PRODUCTIVITY DATA

The health economics outcome and work productivity data will only be collected for subjects in US sites. The following questionnaires will be collected:

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

All data will be analyzed overall, i.e., for the single treatment group neridronic acid 400 mg, for the FAS. All data will be presented in subject data listings.

16.1 Work Productivity and Activity Impairment Questionnaire: CRPS

Answers to the 6 questions of the WAPI: CRPS questionnaire will be descriptively summarized by visit. The answers to question 1 (Are you currently employed: Yes/No?) will be assigned a dichotomous value (1 = Yes; 0 = No) and summarized as a continuous variable, i.e., the proportion of employed subjects will be derived.

16.2 Medical resources utilization and health economics data

The medical resources utilization and health economics questionnaire has 6 categories:

- Hospitalization.
- Emergency room visit.
- Nursing home stay.
- Outpatient care provider contact.
- Home services and help.
- Special product/device/tool.

For the categories hospitalization, emergency room visit, nursing home stay, and special product/device/tool, the use of these services will be descriptively summarized as a categorical variable (Yes/No/Don’t know).

For the categories outpatient care provider contact, and home services and help, the use of each service type within the 2 categories will be descriptively summarized as a categorical variable (Yes/No/Don’t know).

17 INTERIM ANALYSIS

17.1 Interim analysis of efficacy

Not applicable.

17.2 Interim analysis of safety

An external, independent DMC will periodically review safety information from the trial and monitor trial conduct and overall progress.

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

The safety analyses provided to the DMC for each review meeting will be defined in a separate SAP.

18 REFERENCES

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19 CHANGES TO THE SAP

19.1 Changes from pre-final to final version

Not applicable.

19.2 Amendments

Changes were made from Final SAP (Version 1.0) to SAP Amendment 01 (Version 2.0). All the changes are documented in Section 7.3.

20 APPENDIX

20.1 Data derivation and analysis rules

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

20.1.1 General specifications

20.1.1.1 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 (CI) and standard deviation (SD).
- 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 (ICTR) text and are used 1:1 in the body report as well. For analysis of pharmacokinetic data see also Section 20.1.5.

20.1.1.2 Presentation of descriptive statistics

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

Table 6: Presentation of descriptive statistics in clinical trials

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

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

n = number of values; Min = minimum; Max = maximum; SD = standard deviation; Q1 = first quartile; Q3 = third quartile.

20.1.1.3 Presentation of differences and changes

For changes from baseline, the post-baseline value will constitute the minuend and the baseline value the subtrahend, i.e., *change = value - baseline*.

20.1.1.4 Trial day count

The day of allocation/baseline visit / first IMP 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

20.1.1.5 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 ([ ]).

20.1.1.6 Presentation of dates

Where applicable (e.g., in listings), dates will be displayed in ISO8601 format (example: 2014-09-29T12:16, see CDISC 2013 V3.2). In case of incomplete dates, both the original value and the imputed value are displayed.

20.1.1.7 Handling of missing values

At each time point/visit, all subjects still in the trial are reported. Missing values will be taken into account as missing in the analysis. The number of observed values and the number of missing values must sum up to the number of subjects in the trial at the respective time point/visit.

Missing measurements/missing values are identified by the SDTM variable **STAT=ND. If this variable is not recorded (it's a permissible variable) the missing values of **ORRES should be used.

Unless otherwise specified in the SAP, missing values will not be imputed.

20.1.1.8 Visit windows

Not applicable.

20.1.1.9 Assessments of on-treatment-period

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

20.1.1.10 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

20.1.1.11 End of treatment

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

20.1.1.12 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".

20.1.1.13 Kaplan-Meier analysis

No additional specifications.

20.1.1.14 Handling of data from early termination visits

Subjects who discontinue during the trial the before their Visit 11 will be requested to undergo an early termination visit with identical procedures to Visit 11. Procedures done at Visit 11 are listed in the schedule of events of the protocol.

If the last available visit is between Visit 2 and Visit 7, data from the early termination visit will be assigned to the next scheduled visit; otherwise data will be assigned to the nearest scheduled visit based on the trial day of the early termination visit and the planned visit day. The planned visit day is:

- Day 182 for Visit 9 (Week 26).
- Day 273 for Visit 10 (Week 39).
- Day 365 for Visit 11 (Week 52).

In case of equal distance to 2 scheduled visits, the earlier visit will be chosen. If the assigned visit already occurred before the early termination visit, the data will be assigned to the next scheduled visit.

Data from the early termination visit will be analyzed using the re-assigned visits.

20.1.2 Disposition

20.1.2.1 Subject discontinuation

Reasons for subject discontinuation from trial/IMP as specified in the End-of-Trial/Treatment Completer pages of the eCRF will be used.

20.1.2.2 Protocol deviations

Protocol deviations are based on the analysis dataset ADDV. Key and major protocol deviations are retrieved from the respective Study Data Tabulation Model ([SDTM] dataset (SDTM.DV.DVCAT). No further protocol deviations are programmed in the analysis datasets for ADDV (if not otherwise specified in the SAP).

20.1.3 Demographics and other baseline characteristics

20.1.3.1 Subject demographics

Derivation of age

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

Derivation of BMI:

BMI is calculated to 1 decimal place using the following formula:

BMI [KG/M²] = WEIGHT [KG] / HEIGHT²[M]

Derivation of race:

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

20.1.3.2 Other baseline characteristics

Not applicable.

20.1.3.3 Medical history

For CRPS history, time since precipitating event, duration (time since onset of symptoms), and time since diagnosis 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 to 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.

Examples:

Missing date	**Imputed date**
2016-Mar	2016-Mar-*01*
2016	2016-*Jan-01*

20.1.3.4 Prior and concomitant medication or therapy

Prior and concomitant medication is collected as of enrollment in the eCRF 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.

Prerequisite is a complete date/time of first dose of IMP (entered or imputed). For subjects not allocated to treatment, the date/time of first IMP is not defined, and no prior or concomitant status will be assigned to their medications or therapies.

Stop of medication or therapy Date/time	**Condition**	**Category**
Complete date/time is available	Stop date/time is earlier than date/time 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
Missing hours	Day/month/year of stop date are earlier than day/month/year of first dose of IMP	Prior
Missing minutes	Day/month/year/hours of stop date/time are earlier than day/month/year/hours of first dose of IMP	Prior
Otherwise		Concomitant

Medication ticked in the eCRF as "continuing" will be classified as concomitant.

The following rules are used to identify medications or therapies which started after last dose of IMP.

Prerequisite is a complete date/time of last dose of IMP (entered or imputed).

Start of medication or therapy date/time	**Condition**	**Start after last dose of IMP**
Complete date/time is available	Start date/time is later than date/time of last dose of IMP	Yes
Complete date is available	Start date is later than or equal to date of last dose of IMP	Yes
Missing month	Year of start date is later than year of last dose of IMP	Yes
Missing day	Month/year of start date are later than month/year of last dose of IMP	Yes
Missing hours	Day/month/year of start date are later than day/month/year of last dose of IMP	Yes
Missing minutes	Day/month/year/hours of start date/time are later than day/month/year/hours of last dose of IMP	Yes
Otherwise		No

20.1.4 Efficacy analysis

There are no trial-specific definitions for this trial.

20.1.5 Analysis of pharmacokinetic and pharmacodynamic parameters

There are no trial-specific definitions for this trial.

20.1.6 Safety analysis

20.1.6.1 Adverse events

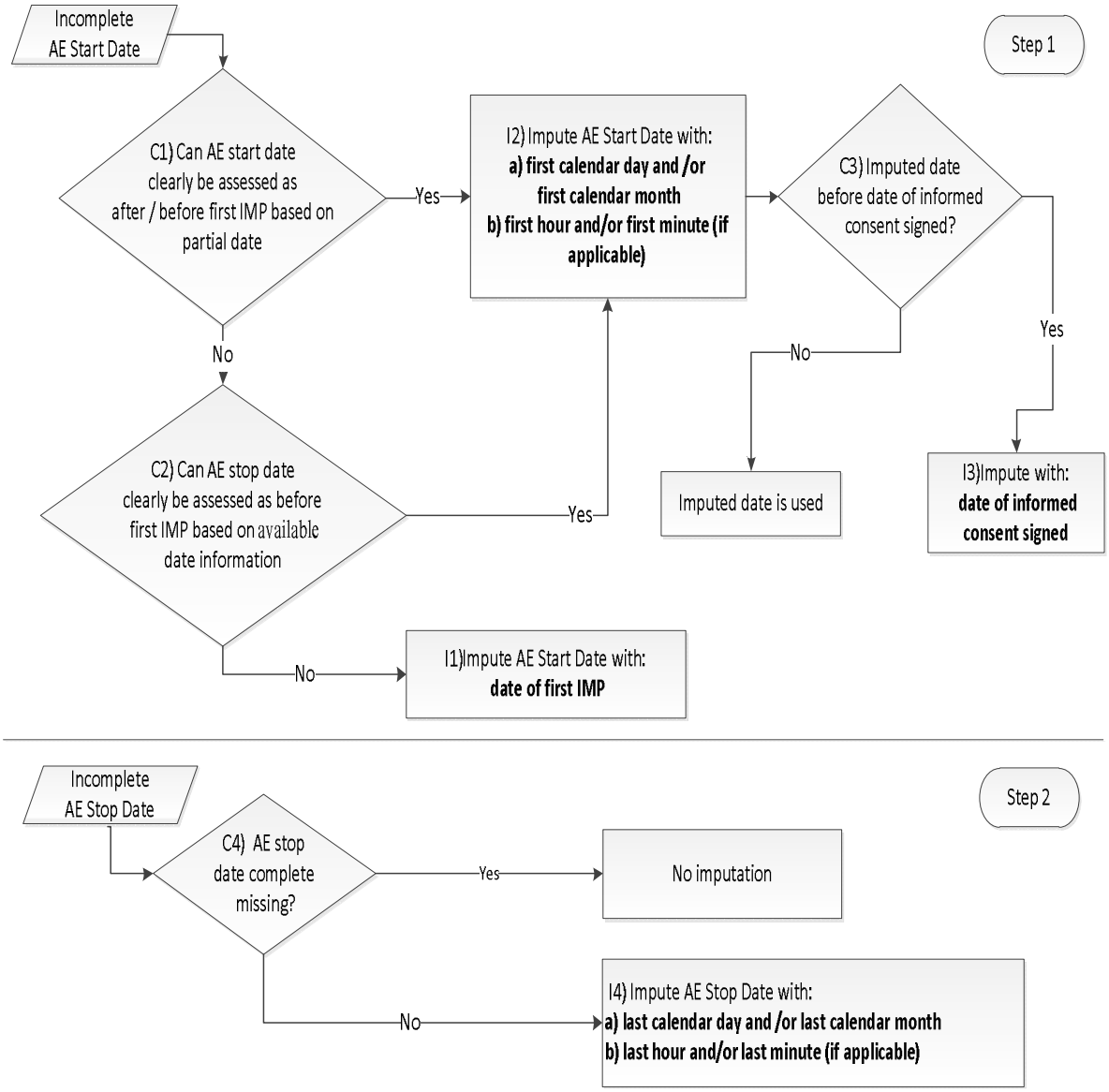
The result of all imputation strategies (e.g., incomplete start dates of adverse events), combination of observations and new derived information (e.g., treatment-emergent flag) must be stored in the Analysis of Data Model (ADaM) data set.

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.

If the number of adverse events with missing date information does not exceed 10% the following imputation strategy is applied.

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

Figure 2: 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

- 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 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 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 first IMP.

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

Not applicable.

List of deaths

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

Time to onset of adverse event

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

Duration of adverse event

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

If duration of 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 eCRF, the duration will be categorized as “continuing”

- Otherwise the duration category will be set to "missing".

Presentation of causal relationship

Causal relationship is ordered in descending order starting with the worst expression:

Expression
certain – probable/likely – possible – conditional/unclassified – unassessable/unclassifiable – unlikely – not related

Subject experiencing a non-serious TEAEs

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

Exposure adjusted incidence rate

In case of missing dates, the imputed dates will be used for calculation of the total exposure time. If the total exposure time equals 0 (thus all TEAEs start with first IMP administration), the total exposure time will be set to 0.1.

20.1.6.2 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 and the additional level "Missing", 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 vs. 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.

Values out of range

For some laboratory parameters, categories such as "positive" and "negative" will be used. The positive category could be further classified as positive "+" or borderline positive "(+)".

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, 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-baseline 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.

20.2 List of statistical output documentation

The complete SAS output of the MMRM analysis of current, average, and worst pain intensities will be included in ICTR Section 16.1.9.

20.3 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.

20.3.1 Reference ranges for vital signs

The reference ranges for vital signs are defined in Table 7.

Table 7: Reference ranges for vital sign 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; LLN = lower limit of normal; mmHg = millimeter of mercury; ULN = upper limit of normal.

20.3.2 Sponsor-defined alert ranges for vital signs

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

Table 8: Sponsor-defined alert ranges for vital sign 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.

20.3.3 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 9: 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
	QTcB interval	<300 msec	>480 msec
	QTcF interval	<300 msec	>480 msec

bpm = beats per minute; ECG = electrocardiogram; QTcB = corrected QT interval (according to Bazett's formula); QTcF = corrected QT interval (according to Fridericia's formula).