Statistical Analysis Plan for the Pooled KF7013-02 & KF7013-04 Interim Analysis for Futility

ELECTRONIC SIGNATURES

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STATISTICAL ANALYSIS PLAN POOLED INTERIM ANALYSIS FOR KF7013-02 AND KF7013-04

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ADaM	Analysis Data Model
CRPS	Complex Regional Pain Syndrome
IMP	Investigational medicinal product
MAR	Missing at Random
MMRM	Mixed Model Repeated Measurements
NRS	Numeric Rating Scale
SAP	Statistical analysis plan
SAS	Statistical analysis software
SDTM	Study Data Tabulation Model

1 INTRODUCTION

This statistical analysis plan (SAP) includes definitions and analysis details for the pooled interim analysis of the 2 Phase III neridronic acid trials, KF7013-02 and KF7013-04 in accordance with the protocols, both dated 14 Mar 2018. The analysis will be performed by an independent statistician in accordance with this SAP and the associated charter.

2 OBJECTIVES OF ANALYSIS

The primary objective of the 2 trials is to demonstrate the superior efficacy of a cumulative dose of 400 mg intravenous neridronic acid versus placebo for the treatment of complex regional pain syndrome (CRPS)-related pain. The primary endpoint is the change from baseline to Week 12 in the average pain intensity score (weekly average of pain values recorded daily in the electronic diary).

An interim analysis is planned after a combined total of approximately 80 subjects in the 2 Phase III trials (KF7013-02 and KF7013-04) have completed Week 12 of treatment and the required data is available in the databases. The interim analysis is for futility only and will be non-binding. The futility criterion will be based on the unblinded comparison of the primary endpoint and will be calculated using identical methods as for the final analysis. If the observed difference in the means of neridronic acid and placebo ($\mu 400 - \mu 0$) is ≥ -0.3 points on the Numeric Rating Scale (NRS), the null hypothesis will not be rejected and the recommendation will be to stop both trials.

The interim analysis will be performed by an independent statistician not otherwise involved in the conduct of the trials and the result will only state the recommendation to stop or continue the Phase III program. No unblinded information will be disseminated to the trial teams. Pending recruitment rates of both trials, it may be decided to forgo the interim analysis or conduct it at a different point in time. Recruitment will continue during the interim analysis.

3 TRIAL DESIGNS

Both trials are identical in design and are multi-site, randomized, double-blind, placebo-controlled, 2-arm, Phase III trials of intravenous neridronic acid in subjects with CRPS. The trials consist of 2 treatment periods. Treatment Period A will be double-blind, whereas Treatment Period B will be open-label. There will be an Enrollment Period (lasting up to 60 days) followed by Treatment Period A (consisting of 4 infusions over 10 days), and a Follow-up Period 1 (lasting from Visit 6 [Week 2] up to Visit 11 [Week 26]. At Visit 11 (Week 26), subjects not meeting the pre-specified criteria to continue into Treatment Period B will continue in the Follow-up Period 2 until Visit 17 (Week 52). The interim analysis will only include data collected up to Visit 8 (Week 12) of the double-blind phase.

Subjects will be randomized to 1 of the 2 treatment groups in a 1:1 ratio stratified by geographic region. The 2 trials will have no overlap in sites (i.e., a site can participate in only one trial).

4 ENDPOINT CRITERIA

The interim analysis will be limited to the average pain intensity score rated on a 11-point NRS (from 0 = “no pain” to 10 = “pain as bad as you can imagine”) reported once daily (in the evening, 24-hour recall) in an electronic diary. The change from the baseline phase (Day -7 to Day -1) to Week 12 will be analyzed.

5 SUBJECT POPULATION

5.1 Interim Analysis Set

The Interim Analysis Set includes the first 80 subjects allocated in the combined trials KF7013-02 and KF7013-04 who have at least 1 investigational medicinal product (IMP) administration, and who have completed the Week 12 visit, or discontinued from the trial prematurely before Week 12.

6 STATISTICAL METHODS

The statistical methods applied will be similar to those planned for the individual trials. Further details can be found in the SAPs of the KF7013-02 and KF7013-04 trials.

6.1 Source of data

Relevant data (demographics, disposition, CRPS history, and pain diary) of subjects included in the Interim Analysis Set will be cleaned and a formal locked snapshot for each trial will be made available. Required Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) domains will be prepared for each of the 2 trials. Subsequently, these will be pooled for the statistical analysis.

The randomization list for the Interim Analysis Set will be provided to the independent statistician separately. The independent statistician will merge the randomization code into the datasets before conducting the analysis. The unblinded datasets will be kept at the independent statistician’s secure location until the closure of the trials.

6.2 Changes in analysis

6.2.1 Description of SAP amendments

Not applicable.

6.3 Description of analysis

In the following sections, a detailed description of variables and statistical methods used in the interim analysis is given. All presentations will be by treatment group and overall, for both trials combined and repeated for each trial separately.

6.3.1 Handling of missing values

Unless otherwise specified in this SAP, missing values will not be imputed. For the handling of missing or incomplete dates, please refer to the trial SAPs.

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

6.3.2 Subject disposition

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

For describing the subject disposition, the following populations will be summarized, overall and by region (with percentage denominator being the number of allocated subjects):

- Subjects allocated.
- Subjects treated and the reasons for not being treated.
- Interim Analysis Set.
- Treatment Period A completers, i.e., subjects who received the full dose of all 4 planned infusions.

6.3.3 Premature terminations

Discontinuations from the trial and from IMP will be presented for the Interim Analysis Set overall, and per site. Reasons for discontinuations from the trial or from IMP will be presented for:

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

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

6.3.4 Subject demographics

Subject demographics are age (years), weight (kg), height (cm), sex, race, ethnicity and will be descriptively summarized.

6.3.5 Baseline characteristics

Not applicable.

6.3.6 Previous and concomitant medication

Not applicable.

6.3.7 Subject medical history

Complex regional pain syndrome history will be descriptively summarized.

Continuous parameters based on date of Visit 1 are:

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

Categorical baseline characteristics are:

- CRPS type (Type I, Type II, Unknown).
- CRPS etiology.
  - Inciting or precipitating event (Missing, Known, Unknown).
  - Fracture, Sprain, Surgery, Crush, Others.
- CRPS location (Left Body Site, Right Body Site, Upper Extremity, Lower Extremity, more than 1 Limb affected).

Except for CRPS type and inciting or precipitating event, multiple answers are possible.

6.3.8 Drug exposure

Exposure will be displayed as the number of subjects receiving 1, 2, 3 or 4 infusions. It will be descriptively summarized.

6.3.9 Analysis of efficacy

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

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

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

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

The statistical analysis will be similar to the primary analysis planned for the individual trials. The primary estimand is the difference in means of the primary efficacy endpoint of 400 mg intravenous neridronic acid compared to placebo for all allocated and treated subjects. This treatment policy or de facto estimand measures the effect of neridronic acid regardless of adherence to treatment or protocol. The primary estimand will be estimated by the analysis of the primary efficacy endpoint for the Interim Analysis Set.

The primary analysis will fit a Mixed Model Repeated Measurement (MMRM) to the change from baseline in the average pain intensity scores from Week 1 to Week 12 recorded once daily in the electronic diary, including the covariate baseline pain intensity score, and the factors geographic region, week, treatment, and treatment-by-week interaction as fixed effects, and subject as random effect. If only one geographic region is represented in the Interim Analysis Set, this factor will be omitted from the model. An unstructured covariance matrix will be used to model the covariance structure, degrees of freedom will be estimated using the Kenward-Roger approximation. The primary efficacy analysis will be performed using the contrast, i.e., the mixed model Wald test, of neridronic acid 400 mg versus placebo at Week 12 of the treatment, week and treatment-by-week interaction term of the mixed effects model described above. Model-based parameter estimates (least square means), standard errors, 95% confidence intervals, and p-values will be tabulated. This analysis will be performed using only the observed values without imputation of missing values.

The point estimate for the observed difference in the means of neridronic acid and placebo will be calculated as the difference between the respective least squares means. If this estimate is ≥-0.3 points on the NRS, futility will be concluded and the recommendation will be to stop both trials.

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

A descriptive summary of the weekly averages and the changes from baseline will be generated by treatment group. A graphical plot of the model-based estimates and the 95% confidence interval of the change from baseline of the average pain intensity scores over the 12-week trial period will be created. Both treatments will be presented in one plot by week.

6.3.10 Analysis of adverse events

Not applicable.

6.3.11 Analysis of laboratory parameters

Not applicable.

6.3.12 Analysis of vital signs

Not applicable.

6.3.13 Analysis of further safety parameters

Not applicable.

7 STATISTICAL OUTPUT DOCUMENTATION

The statistical output documentation will contain the original SAS-output for all analyses described in this SAP. The output will be kept at the independent statistician's secure location until the closure of the trials, upon which they will be transferred to the sponsor.

8 CODING

Not applicable.

9 STATISTICAL SOFTWARE

All summary tables and statistical analyses are generated using SAS Version 9.4 or higher.

10 REFERENCES

Mallinckrodt CH, Lane PW, Schnell D, Peng Y, Mancuso JP. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. Drug Inf J 2008; 42 (4): 303-19.

11 APPENDIX

Not applicable.

11.1 Reference ranges for laboratory parameters

Not applicable.

11.2 Sponsor defined ranges for laboratory parameters

Not applicable.

11.3 Table shells, figure shells, and listings

A separate document containing the shells (i.e., without real data) for the tables, listings and figures will be prepared in parallel to the SAP.