Statistical Analysis Plan

Trial Title:
An open-label, multicentre, extension trial to assess the safety of redosing of intravenous iron isomaltoside (Monofer®)

Trial ID:

P-Monofer-IDA/CKD-EXT-01

Phase III Trial

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The signatures below confirm that the signees have read, understood and approved of the contents of the present statistical analysis plan.

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1 List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ASAT	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CRF	Case Report Form
DBL	Data Base Lock
ECG	Electrocardiogram
ESA	Erythropoiesis Stimulating Agents
FAS	Full Analysis Set
ITT	Intention-To-Treat
Hb	Haemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of Subjects
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event

2 Introduction

The statistical analysis plan (SAP) for the P-Monofer-IDA/CKD-EXT-01 trial is based on the final protocol 2.0 dated 14 June 2017.

The SAP describes in detail the analyses to be conducted and highlights any deviations from the analysis described in the protocol (see section 8). Deviations from methods described in this SAP, if any, will be specified in the clinical trial report.

Throughout this SAP treatment and baseline refers to treatment and baseline, respectively in this extension trial, unless otherwise specified.

Before releasing data for final analysis, one or more data review and classification meetings will be held to classify subjects with respect to analysis populations. The product of the classification meetings will be a detailed description of the analysis populations, and the number and nature of unresolved data queries will also be reported.

The analyses will be performed based on:

- The clinical database, which includes the electronic Case Report Forms (CRF)
- List of protocol deviations
- Analysis populations documented at the classification meetings

Reporting of the trials will be after the date of last subject last visit.

3 Trial Characteristics

3.1 Trial Objectives

3.1.1 Primary Objective

The primary objective of the trial is to evaluate the safety of IV iron isomaltoside after redosing.

3.1.2 Secondary Objectives

The efficacy objective of the trial is to evaluate the effect of iron isomaltoside on:

- Increase in haemoglobin (Hb)
- Other relevant iron related biochemical parameters

3.2 Trial Design

The trial is a prospective, open-label, multi-centre, extension trial of the lead-in trials; P-Monofer-IDA-01, P-Monofer-IDA-03, and P-Monofer-CKD-04.

The trial is a one-armed trial and all subjects will receive iron isomaltoside (Monofer®).

Table 1: Flow Chart

Visit	**1 Screening**	**2 Baseline**	**3**	**4**	**5**
Time (weeks)	**-2**	**0**	**2**	**13**	**26**
Visit window (days)		-	**± 2**	**± 3**	**± 4**
Informed consent	X				
Demographics	X				
In/exclusion criteria	X	X			
Eligibility lab tests	X[c]				
Pregnancy test, if relevant		X			
Medical history, including specific assessment of history of myocardial infarction, stroke, or congestive heart failure		X	X	X	X
Concomitant medication		X	X	X	X
Physical examination		X			X
Height		X			
Weight		X			X
Vital signs[a]		X	X	X	X
ECG[a]		X	X	X	X

Safety lab tests		X	X	X	X
Efficacy lab tests		X	X	X	X
Treatment with iron isomaltoside		X			
Adverse events		X	X	X	X
Final visit form[b]					X

a. *For details of the assessment, please see Section 7.3.3.*

b. *The final visit form may be filled in at any time of the trial if the subject is withdrawn.*

c. *Laboratory tests taken at visit 6 of the lead-in trials P-Monofer-IDA-03 and P-Monofer-CKD-04 will be considered as screening values for the extension trial if they are collected ≤14 days before the screening visit.*

3.3 Subject included

3.3.1 Sample Size Determination

No sample size calculations have been performed for this extension trial.

A target of 100 subjects will be recruited at selected sites with at least 25 subjects from P-Monofer-IDA-01 and P-Monofer-IDA-03 combined and at least 25 from P-Monofer-CKD-04. The distribution of subjects from each of the three trials does not need to be equal and the subjects will be enrolled consecutively based on the enrolment criteria until 100 subjects have been enrolled.

4 Analysis Populations

The following 4 analysis sets for subjects requited in this extension trial are defined and will be used in the analyses of the data:

- Safety analysis set: The safety analysis set will include all subjects who received at least one dose of the trial drug.
- Intention to treat (ITT) analysis set: The ITT analysis set will include all subjects, with the exception of screening failures.
- Full Analysis Set (FAS): The FAS will consist of all subjects who received at least one dose of the trial drug in the lead-in trial (i.e. does not violate inclusion criteria 2), and have at least one post baseline Hb assessment.
- Per protocol (PP) analysis set: The PP analysis set will include all the subjects in the FAS who do not have any major protocol deviation of clinical or statistical significance. Major protocol deviations are defined in Section 4.1.

The classification of the subjects will be performed before database lock (DBL).

The primary analysis population for efficacy evaluation is the ITT analysis set. All efficacy endpoints will be presented using the ITT. If the FAS contains less than 90% of the subjects in the ITT set, then Hb will in addition be presented using FAS. Similar if the PP set contains less than 90% of the subjects in FAS (or ITT, if FAS is not presented), then Hb will in addition be presented using the PP analysis set.

4.1 Major protocol deviations

Deviations from the protocol will be registered as protocol deviations. Before DBL all protocol deviations will be evaluated and classified as minor, major, or GCP deviations. Protocol deviations classified as major will lead to exclusion from PP analysis set. The decisions will be documented.

The following will be assessed as major protocol deviation:

- Out of visit window of ≥ 30 days after the final visit (i.e. ≥ 212 days after baseline)
- Intake of prohibited medication
- Treatment compliance outside the 80-120 % range
- Other protocol deviations which are assessed as having a clinically or statistically significant effect

All major protocol deviations will be listed by subject and lead-in trial. Separate listings will be made for the ITT analysis set of visits 6 outside window of 14 days or more, intake of prohibited medication and treatment compliance outside range. Protocol deviations will be summarised by classification and category. The summary table will present number and percentages of subjects with a deviation and number of deviations.

4.1.1 Prohibited Medication

The following medication and non-drug therapy is not allowed:

- Any premedication (e.g. antihistamine or steroids) before administration of the trial drug. Daily treatment for e.g. allergy or asthma this is not considered as "premedication"
- Any iron supplementation other than investigational drug (nutritional supplementation including iron is allowed unless it is assumed as treatment of the subject's anaemia)
- Blood transfusion
- Erythropoiesis Stimulating Agents (ESA), unless the subject was treated with ESA in the lead-in trial or has received a stable dose (+/- 20 %) 4 weeks before the screening visit in this trial.

5 Planned Statistical Methods

5.1 Statistical Considerations

No formal hypotheses will be tested in this 6 months, one-armed, safety extension trial.

Baseline is defined as the last assessment with available data prior to the first administration of trial medication.

Categorical data will be summarized, using number and percentages of subjects. For calculation of percentages the denominator will be the number of subjects in the analysis set, unless otherwise stated. Numerical data will be presented using the number of subjects (n), mean, standard deviation (SD), median, lower quartile, upper quartile, minimum and maximum. Both the absolute values and the change from baseline will be presented, unless stated otherwise.

Descriptive statistics for all endpoints will be presented overall and by lead-in trial and by week (if applicable) using observed cases, i.e. no imputation of missing data will be performed. All listings will be by lead-in trial and subject id unless stated otherwise.

5.2 Subject Disposition

An overall summary table of the subject disposition will be prepared with number and percentages of subjects in the following categories (and sub-categories):

- Screened subjects
- Analysis sets (ITT, safety analysis set, FAS, and PP analysis set)
- End of study status
- Withdrawn from trial including reasons

For calculation of the percentages the denominator will be number of subjects in the ITT.

Subject disposition will in addition be presented by lead-in trial. All information will be listed. Screening failures will be listed.

5.3 Baseline Characteristics and Demographics

Demographics and baseline characteristics consist of age, gender, ethnic origin, and smoking habits. Age will in addition be grouped into: 18-64 years, 65-84 years and above 84 years. Demographics will be listed and summarized using descriptive statistics, overall and by lead-in trial for the ITT analysis set. Age, Age groups and sex will in addition be presented by the FAS, safety analysis set and PP population.

5.4 Medical History

Relevant medical history is collected and will be summarised and listed. The summaries will be made by system organ class (SOC) and preferred term and by preferred term for the ITT analysis set. Separate summary and listing will be made of underlying disorder causing IDA.

6 Exposure and Other Dosing Information

6.1 Exposure

Dose and compliance will be summarized using descriptive statistics and presented for the safety analysis set overall and by lead-in trial.

For actual dose will be presented including dose category, dose in mg, number of doses and compliance.

Compliance will be calculated as: $$\frac{100 * \text{actual dose}}{\text{planned dose}}$$

All information will be listed by lead-in trial and subject. Furthermore, subjects out of the treatment compliance range of 80-120 % will be listed.

6.2 Concomitant medication

Concomitant medication at baseline and changes in concomitant medication during the trial will be recorded. All concomitant medication will be summarised and listed using the ITT analysis set. The summaries will be made by anatomical therapeutic chemical (ATC) term The listing will be by lead-in trial and subject.

7 Statistical Methodology for Primary and Secondary Endpoints

7.1 Analysis and Presentation of the Primary Endpoint

The primary endpoint is the number of adverse drug reaction (ADR), defined as adverse events (AEs) that are related or possible related to trial drug.

Overall number and percentages of subjects with ADRs and number of ADRs will be summarized overall and by lead-in-trial, including two-sided 95 % exact Clopper-Pearson confidence limits (CL) for the number of subjects reporting ADRs.

7.2 Secondary Safety Endpoints

The secondary safety endpoints are the following:

- Serious or severe hypersensitivity reaction starting on or after the treatment with iron isomaltoside (i.e. treatment-emergent). The hypersensitivity terms are defined as standardised Medical Dictionary for Regulatory Activities query (SMQ) terms (including four additional terms) in protocol Appendix A.
- Composite cardiovascular AEs starting on or after the treatment with iron isomaltoside (i.e. treatment-emergent). The adjudicated composite AEs includes the following:
    - Death due to any cause
    - Non-fatal myocardial infarction
    - Non-fatal stroke
    - Unstable angina requiring hospitalization
    - Congestive heart failure requiring hospitalization or medical intervention
    - Arrhythmias
    - Hypertension
    - Hypotension
- Time to first composite cardiovascular safety AE
- Serum (s-) phosphate < 2 mg/dL at any time from baseline to month 6

Additional safety assessments are physical examinations and measurements of vital signs, height, weight, electrocardiogram (ECG), and safety laboratory parameters.

7.3 Analysis and Presentation of the Safety Endpoints

7.3.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) current version. AEs will be regarded as treatment emergent AEs (TEAEs) if they occur after administration of iron

isomaltoside or occur before dosing and increase in severity after dosing. AEs that increase in severity from before till after dosing will be identified by means of Data Management Audit Trail. Non-treatment emergent AEs (Non-TEAE) are defined as AEs collected in the current trial, before dosing and does not increase in severity from before till after dosing. There will be more than 5 half-lives between dosing in the lead-in trial and screening in the current trial, thus none of the AEs will be regarded as related to previous treatment.

An overall summary table by treatment will be made. The overall summary table will include total number of events, total number of subjects, and proportion of subjects reporting AEs, non-TEAEs, TEAEs, Treatment emergent serious adverse events (SAEs), Fatal SAEs, ADRs, serious adverse reactions (SAR), TEAEs by severity, and TEAEs by outcome.

All TEAEs will be summarised by SOC and preferred term (PT). The summaries will include number of events, number of subjects, and proportion of subjects reporting these events and will be tabulated overall and by lead-in-trial for:

- TEAEs
- Non-serious TEAEs, frequency ≥ 5% (or lower frequency as applicable)
- Treatment emergent SAEs
- TEAEs by severity (mild, moderate, severe)
- TEAEs by relationship (related, possible, unlikely, not related, unknown)
- ADRs
- SARs
- Composite cardiovascular TEAEs
- Serious or severe hypersensitivity reactions
- Hypersensitivity reactions

A two-sided 95 % exact Clopper-Pearson confidence limit (CL) for the overall number of subjects reporting SARs will be constructed.

The following listings of AEs will be made based on the safety analysis set:

- Non-TEAEs
- TEAEs (non-serious and serious)
- TESAEs
- ADRs (including SUSARs)
- AEs leading to dose reduction or withdrawal from treatment
- Fatal SAEs
- Serious or severe hypersensitivity reactions
- Hypersensitivity reactions
- Composite cardiovascular AEs

In addition, a listing of SAEs for subjects not in the safety analysis set will be made.

All data from adjudication review will be listed.

Time to first composite cardiovascular AE is defined as the actual time in days from date of treatment till the date of the adjudicated AE. For subjects not reporting a composite cardiovascular AE, the time will be censored at the date of the last attended visit.

The time to first composite cardiovascular AEs will be estimated using the Kaplan-Meier method and presented in a plot.

7.3.2 Serum Phosphate

Subjects with serum (*s*-) phosphate < 2 mg/dL at any time from baseline to month 6 will be listed. The listing will include phosphate values for all weeks. The data will in addition be presented in a longitudinal plot.

7.3.3 Other Safety Assessments

ECG and Physical Examination

Standard 12 lead ECG and Physical examination is assessed at baseline and at week 26. At baseline, two ECGs will be recorded; one before administration of the trial drug and one approximately 30 minutes after start of the dosing. ECG and each body system of the physical examination will be evaluated as normal or abnormal, and if abnormal clinical significant or not.

The 3 categories of ECG will be presented overall by shift tables from baseline (before treatment) till after dosing and week 26. The shift tables will be repeated by lead in trial. Similar shift tables from baseline till week 26 will be made for physical examination worst case. All data will be listed.

Vital Signs

Vital signs (heart rate, systolic and diastolic blood pressure) will be measured at baseline, weeks 2, 13, and 26. At baseline, vital signs will be measured at the following time points:

- Approximately 0-10 minutes before infusion, during infusion, 5-15 minutes, and 20-40 minutes after the infusion has ended

Vital signs will be summarized by treatment, week and time point, including change from pre- infusion at the treatment visit. The summary tables will be repeated by lead in trial. Vital signs will be listed by subject.

Height and Weight

Height is measured at baseline. Weight is measured at baseline and at the final visit.

Height will be summarised by treatment for the pooled data overall, and by lead in trial.

Weight will be presented in summary tables by treatment and week including change from baseline. This will be made for the pooled data overall, and by lead in trial. All data will be listed by subject.

Laboratory Safety Data

Safety laboratory parameters (haematology and biochemistry) are measured at baseline and at week 2, 13, and 26.

Laboratory safety data will be summarised using descriptive statistics, including means, medians, SDs, and minimum and maximum by week, overall and by lead-in-trial. Furthermore, changes from baseline will summarised. In addition, laboratory safety data will be plotted using boxplots by week.

Values outside normal ranges will be flagged. All safety laboratory data will be listed by lead-in-trial and subject including eligibility laboratory assessments. Clinical significant laboratory will be listed including the corresponding AE.

7.4 Analysis and Presentation of the Secondary Efficacy Endpoints

The secondary efficacy endpoints are the following:

- Change in Hb from baseline to week 2 and months 3 and 6
- Change in s-ferritin, transferrin saturation (TSAT), and s-iron from baseline to week 2 and months 3 and 6

Change in Hb from baseline to week 2 and months 3 and 6 will be summarised by week using descriptive statistics overall and by lead-in trial for the ITT, and for the FAS and PP analysis sets, if applicable. Furthermore, change from baseline for the lead-in trial to current baseline, week 2 and months 3 and 6 including absolute Hb values will be summarised. Change in Hb concentrations over time will be presented using mean plots overall and by lead-in trial. Serum (s)-ferritin, TSAT and s-iron will be presented in similar ways using the ITT analysis set, only.

The efficacy data will be listed by lead-in-trial, subject and time point.

7.5 Handling of Missing Values

No imputation of missing values will be applied.

7.6 Multiplicity adjustments

In this one-armed extension trial, no formal statistical analyses will be performed and there will be no adjustment for multiplicity.

7.7 Sub-group and Centre Effects

Summary tables of demographics, efficacy and secondary safety endpoints will be prepared overall and by lead-in trial.

No effect of centres will be evaluated.

7.8 Interim Analysis

No interim analysis is planned.

8 Deviations from Protocol

The below describes the deviation in statistical methods as compared to the protocol text.

- In the protocol section 15.3 it is stated that the ITT analysis set will include all subjects. This has been changed to: The ITT analysis set will include all subjects, with the exception of screening failures.

- In the protocol section 15.5 it is stated that summaries will be prepared with respect to two baselines: Baseline in lead-in trial, and baseline in this extension trial. This will only be applied to the efficacy endpoints.
- In the protocol section 15.6 it is stated that the incidence of treatment-emergent ADRs and SARs will be presented, including two-sided 95 % CI. Instead a two-sided CI around the number of subjects with ADRs and SARs, respectively will be constructed.
- In the protocol section 15.6 it is stated that number of subjects who experience an ADR including SUSARs will be compared between treatment groups. This is not applicable in this one-armed trial.

9 Software

All statistical calculations described in this SAP will be done by [redacted] using SAS, release 9.4 or later (SAS Institute, Cary, NC, USA).

10 Reference List

Not applicable.