

Sponsor:	Pharmacosmos A/S	Date:	12MAR2018
Drug/Project:	Monofer	Version:	Final 2.0
Trials:	P-Monofer-IDA-04 P-Monofer-IDA-05	<b>Statistical Analysis Plan</b>	

## **Statistical Analysis Plan**

Trial IDs:  
P-Monofer-IDA-04 and P-Monofer-IDA-05

*Randomized, open-label, comparative trials comparing the incidence of hypophosphatemia in relation to treatment with iron isomaltoside and ferric carboxymaltose in subjects with iron deficiency anaemia*

### **Phase III Trials**

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**Statistical Analysis Plan**

## Signature page

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## 1 List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
cFGF23	C-terminal Fibroblast Growth Factor 23
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CSR	Clinical Study Report
CTX	Carboxy-terminal Collagen Crosslinks
ECG	Electrocardiogram
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
Hb	Haemoglobin
IDA	Iron Deficiency Anaemia
iFGF23	Intact Fibroblast Growth Factor 23
ITT	Intention-To-Treat
LLOQ	Lower Limit Of Quantification
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Maximal Expiratory Pressure
MIP	Maximal Inspiratory Pressure
MMRM	Mixed Models for Repeated Measures
PCS	Physical Component Summary
PINP	Propeptide of Type I Collagen
PP	Per Protocol

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PT	Preferred Term
PTH	Parathyroid Hormone
QoL	Quality of Life
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SF-36	Short Form - 36
S-ferritin	Serum-ferritin
SMQ	Standardised Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class
S-phosphate	Serum-phosphate
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TSAT	Transferrin Saturation
VAS	Visual Analogue Scale

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## 2 Introduction

The generic statistical analysis plan (SAP) for the identical trials P-Monofer-IDA-04 and P-Monofer-IDA-05 is based on the final protocols, both version 3.0 including amendment 2 dated 29 November 2017.

Reporting of each trial will be done individually after the date of last subject last visit of the trials.

A combined analysis is planned, which will be done when both trials are finalised. The trials will be reported without the combined analysis, which will be included as an appendix to both clinical study reports (CSRs).

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

Before releasing data for final analysis, one or more data review and classification meeting will be held to review protocol deviations in order 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 analysis is performed based on:

- The clinical database, which includes the electronic Case Report Forms (CRF)
- List of protocol deviations
- Analysis populations documented in the data base lock minutes.

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### 3 Trial Characteristics

#### 3.1 Trial Objectives

##### 3.1.1 Primary objective

The primary objective of the trials is to compare the incidence of hypophosphatemia in subjects with Iron Deficiency Anaemia (IDA) treated with iron isomaltoside or ferric carboxymaltose.

##### 3.1.2 Secondary safety objectives

The secondary safety objectives of the trials are to compare the effects of iron isomaltoside and ferric carboxymaltose treatment in subjects with IDA on the following:

- (1) Incidence of severe hypophosphatemia
- (2) Time with hypophosphatemia
- (3) Proportion of subjects with hypophosphatemia at the last visit
- (4) Absolute [Δ] and relative [%] changes in serum-phosphate (s-phosphate)
- (5) Fractional phosphate urinary excretion
- (6) Intact Fibroblast Growth Factor 23 (iFGF23), C-terminal FGF23 (cFGF23), vitamin D (25, 1.25, 24.25), Parathyroid Hormone (PTH), and ionized calcium
- (7) Adverse Events (AEs) and biochemical safety parameters

##### 3.1.3 Secondary efficacy objectives

The secondary efficacy objective of the trials is to compare the effects of iron isomaltoside and ferric carboxymaltose treatment in subjects with IDA on Haemoglobin (Hb), serum-ferritin (s-ferritin), and Transferrin Saturation (TSAT).

##### 3.1.4 Additional objectives

In addition to the trials primary and secondary objectives, the effect of iron isomaltoside and ferric carboxymaltose will be investigated purely exploratory on the following:

- (1) Biochemical bone/muscle markers
- (2) Fatigue symptoms
- (3) Quality of Life (QoL)
- (4) Bone pain
- (5) Muscle strength

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### 3.2 Trial Design

The trials are randomized, open-label, comparative trials. The trials duration for the individual subjects will be approximately 9 weeks (including a 28 days screening period) and each subject will attend 8 visits. Subjects with IDA will be stratified according to type of underlying disease (women with IDA due to gynaecological blood losses; yes/no) and screening s-phosphate level (< 3.5 mg/dL or  $\geq$  3.5 mg/dL), and randomized 1:1 to one treatment course of one of the following treatments:

- Group A: iron isomaltoside (1000 mg infusion at baseline, cumulative dose: 1000 mg)
- Group B: ferric carboxymaltose (750 mg infusion at baseline and day 7, cumulative dose: 1500 mg)

It is intended that 50 % of the recruited subjects are women with IDA due to gynaecological blood losses.

**Table 1: Activities Flow Chart**

Visit	1 Screening	2 Baseline	3	4	5	6	7	8
Time (days)	Max -28	0	1	7	8	14	21	35
Visit window (days)	-	-	+1	+1	+1	$\pm 2$	$\pm 3$	$\pm 3$
Informed consent	X							
Demographics	X							
In/exclusion criteria	X	X						
Eligibility lab tests <sup>a</sup>	X							
Pregnancy test, if relevant		X						
Medical history		X	X	X	X	X	X	X
Concomitant medication		X	X	X	X	X	X	X
Physical examination		X <sup>b</sup>						X
Height <sup>b</sup>		X						
Weight		X <sup>b</sup>						X
Vital signs <sup>c</sup>		X		(X)				
Randomization		X						
ECG <sup>c</sup>		X	X	X	X	X	X	X
FACIT Fatigue Scale		X				X		X
SF-36 questionnaire		X				X		X
Bone pain intensity/VAS		X				X		X
Grip strength/Jamar hand dynamometer		X				X		X

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Visit	1 Screening	2 Baseline	3	4	5	6	7	8
Time (days)	Max -28	0	1	7	8	14	21	35
Visit window (days)	-	-	+ 1	+ 1	+ 1	± 2	± 3	± 3
1 kg arm lift test		X				X		X
30 sec chair stand test		X				X		X
MIP and MEP		X				X		X
Vitamin E		X						
Safety lab tests		X	X	X	X	X	X	X
Efficacy lab tests		X	X	X	X	X	X	X
Exploratory lab tests		X	X	X	X	X	X	X
Urine sample		X	X	X	X	X	X	X
Treatment with iron isomaltoside <sup>d</sup> or		X						
Treatment with ferric carboxymaltose <sup>d</sup>		X		X				
Adverse events		X	X	X	X	X	X	X
Final visit form <sup>e</sup>								X

- a. If the subject's Hb value is unknown to the Investigator, pre-screening with HemoCue Hb test may be performed.
- b. Physical examination, height, and weight may be measured between the screening and baseline visit.
- c. For details of the assessment, please see the protocol Sections 7.8 (vital signs) and 7.9 (ECG).
- d. All trial assessments should be done before administration of the trial drug unless otherwise stated in the protocol Section 7.
- e. The final visit form may be filled in at any time of the trial if the subject is withdrawn.

### 3.3 Subject included

#### 3.3.1 Sample Size Determination

Data from a previous trial conducted with iron isomaltoside 1000 mg suggests that the incidence of hypophosphatemia in a gynaecology population with/without heavy uterine bleeding can be expected to be approximately 10 % (P-Monofer-IDA-01, 1000 mg; n=3/29=10.3 %, 95 % Confidence Interval (CI) = 2-27 %, gynaecology subgroup; n = 1/10 = 10.0 %, 95 % CI = 0-45 %). For ferric carboxymaltose, the incidence has been observed to be 40-70 % (e.g. Wolf *et al.*, 2013; n = 10/17 = 59 %, 95 % CI = 33-82 %). The significance level is set to 5 %, and the power is set to 80 %. Assuming incidences of 15 % for iron isomaltoside and 40 % for ferric carboxymaltose, 49 subjects in each treatment group is required to detect a difference between the treatment groups.

To account for the uncertainty, and to gain more safety information, 60 subjects per treatment group will be randomized in both trials.

## 4 Analysis Populations

The following data analysis sets are defined in the protocol:

- Intention to Treat (ITT) analysis set: The ITT analysis set will include all randomized subjects. This will be the primary analysis set for evaluating efficacy. Subjects will be included as randomized.
- Safety analysis set: The safety analysis set will include all subjects who received at least one dose of the trial drug. This will be the analysis set for evaluating safety. Subjects will be included as treated.
- Full Analysis Set (FAS): The FAS will consist of all randomized subjects who received at least one dose of the trial drug and have at least one post baseline Hb assessment. Subjects will be included as randomized.
- Per Protocol (PP) analysis set: The PP analysis set will include all subjects in the FAS who do not have any major protocol deviation of clinical or statistical significance. Major protocol deviations are defined in the trial protocols Section 17.3.

The primary analysis population is the safety analysis set, which will be used for all safety evaluations. ITT analysis set will be used for all efficacy evaluations. FAS and PP analysis set will be used for the analysis of Hb.

## 5 Planned Statistical Methods

### 5.1 Statistical Considerations

Baseline is defined as the last assessment with available data prior to the first administration of trial medication. The following visits are scheduled:

**Table 2 Visit schedule**

Visit	1 Screening	2 Baseline	3	4	5	6	7	8
Time (days)	Max -28	0	1	7	8	14	21	35
Visit window (days)	-	-	+ 1	+ 1	+ 1	± 2	± 3	± 3

The visits will be labelled by screening, baseline and scheduled day. Categorical data will be summarized by treatment, using number and percentages of subjects. For calculation of percentages, the denominator will either be the number of subjects in the analysis set or the number of subjects in the analysis set with non-missing values. Continuous 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.

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Descriptive statistics for all endpoints will be presented by treatment group and day, if applicable, using observed cases, i.e. no imputation of missing data will be performed. Missing data for time to event endpoints is handled using censoring.

Values below lower limit of quantification (LLOQ) will be substituted by 0.5\*LLOQ in tables and figures.

In the following, strata are defined as *Type of underlying disease: women with IDA due to gynaecological blood losses (yes or no) and screening s-phosphate level (< 3.5 mg/dL or ≥ 3.5 mg/dL)*.

### 5.1.1 Key methods

The following two methods will be used for several endpoints.

#### Cochran-Mantel-Haenszel

Iron isomaltoside will be compared to ferric carboxymaltose by estimation of the risk difference of a parameter and the associated 95 % Newcombe CI adjusting for strata using the Cochran-Mantel-Haenszel (CMH) method. The risk difference, 95 % CIs and the corresponding p-value will be presented.

#### Mixed Models for Repeated Measures

Change in a parameter from baseline will be analysed using a Restricted Maximum Likelihood (REML)-based Mixed Models for Repeated Measures (MMRM) approach. All subjects with post-baseline data will be included with their observed data. Subjects without post-baseline values will have change from baseline set to 0 at the first post-baseline visit.

The model will include the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), strata, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors. If, unexpectedly, this analysis fails to converge, the following structures will be applied, in the following order; first-order ante-dependence, heterogeneous compound symmetry, compound symmetry. The comparisons will be the contrasts between iron isomaltoside and ferric carboxymaltose at the day or days in question based on the least squares means for the treatment-by-day interaction effect. The estimated mean differences based on this model will be reported with two-sided symmetric 95 % CIs and corresponding p-values. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

## 5.2 Subject Disposition

A summary table of the subject disposition by planned treatment and overall and also by strata will be prepared with number and percentage of subjects in the following categories (and sub-categories):

- Screened, randomised and exposed subjects
- Analysis sets (ITT, safety, FAS and PP analysis set)
- End of study:
  - Completed
  - Withdrawn

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- Reason for withdrawal:
  - Adverse event
  - Screen failure
  - Withdrawal by subject
  - Lost to follow-up
  - Protocol deviation
  - Investigator decision
  - Sponsor request
  - Other

All randomised subjects by planned treatment will be used as denominator in the table.

All disposition information will be listed. Screening failures and major protocol deviations will be listed by subject. Visits outside visit window will be listed. Subjects with at least three visits outside visit window will be listed.

### 5.3 Baseline Characteristics and Demographics

Demographics and baseline characteristics consist of age, gender, race, ethnicity, height, smoking habits, and strata. Demographics and baseline characteristics will be listed and summarized using descriptive statistics, by treatment, and by treatment and strata for the safety and if different, then also for the ITT analysis set.

### 5.4 Medical History and IDA-Underlying Disease

Relevant medical history is collected. Changes in medical history will be recorded at the subsequent visits during the trials. Worsening of symptoms or diseases is recorded as AEs.

Medical history and IDA-underlying disease will be summarised and will also be listed by subject for the safety analysis set.

## 6 Exposure and Other Dosing Information

All descriptive data will be presented by treatment for the safety analysis set.

### 6.1 Exposure

Dose and compliance will be summarised. Planned and actual dose in mg, number of doses and compliance will be presented. Treatment interruptions and restarts will be listed.

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

All information will be listed. Also subjects out of the treatment compliance range of 80-120 % will be listed.

### 6.2 Concomitant medication

Concomitant medication is recorded at baseline and during the trial.

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Concomitant medication will be summarised and will also listed by subject. Subjects using prohibited medication during the trials will be listed.

## 7 Statistical Methodology

The safety analysis set will be used for all safety endpoints and the ITT analysis set will be used for all efficacy endpoints if nothing else is stated.

### 7.1 Analysis and Presentation of the Primary Endpoint

The primary endpoint is

- Incidence of hypophosphatemia, defined as *s*-phosphate < 2 mg/dL, at any time from baseline to day 35.

#### 7.1.1 Incidence of hypophosphatemia at any time from baseline to day 35

The incidence of hypophosphatemia at any time from baseline to day 35 will be tabulated and exact 95 % CI will be estimated for each treatment group.

Iron isomaltoside will be compared to ferric carboxymaltose by CMH as described in section 5.1.1..

Two sensitivity analyses will be presented:

- The treatment groups will be compared by a logistic regression model with treatment and strata as factors and baseline *s*-phosphate as covariate. The estimated treatment ratio of iron isomaltoside versus ferric carboxymaltose will be presented with 95 % CIs and corresponding p-value.
- The treatment groups will also be compared by Fisher's exact tests where the p-value will be presented

All subjects in the safety analysis set will be included in the analyses.

If very few subjects are present in one of the strata, similar analyses will be presented, but where two of the categories are grouped.

The number and percentage of subjects with hypophosphatemia will be presented by treatment and visit, and by treatment, strata and visit using bar chart. The *s*-phosphate data will be listed by subject. Subjects with *s*-phosphate < 2 mg/dL will be listed.

### 7.2 Analysis and Presentation of the Secondary Safety Endpoints

The secondary safety endpoints are the following:

- Incidence of *s*-phosphate < 1.0 mg/dL at any time from baseline to day 35
- Time with hypophosphatemia (i.e. time with *s*-phosphate < 2.0 mg/dL) from baseline to day 35
- Proportion of hypophosphatemia at day 35
- Absolute [Δ] and relative [%] changes in *s*-phosphate from baseline to day 1, 7, 8, 14, 21, and 35
- Fractional phosphate urinary excretion at day 1, 7, 8, 14, 21, and 35
- Change in iFGF23, cFGF23, vitamin D (25, 1.25, 24.25), PTH, and ionized calcium from baseline to day 1, 7, 8, 14, 21, and 35
- Type and incidence of AEs
- Serious or severe hypersensitivity reaction starting on or after the first dose of randomized treatment (i.e. treatment emergent). The hypersensitivity terms are defined as standardised Medical Dictionary for Regulatory Activities query (SMQ) terms (including four additional terms) in the protocol in Appendix A.

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### 7.2.1 Incidence of s-phosphate < 1.0 mg/dL at any time from baseline to day 35

The incidence of s-phosphate < 1.0 mg/dL at any time from baseline to day 35 will be analysed and presented like the primary endpoint using CMH as described in section 5.1.1 and the sensitivity analyses described in section 7.1.1.

The number and percentage of subjects with s-phosphate < 1.0 mg/dL will be summarised by treatment and day. The s-phosphate data will be listed by subject as mentioned in section 7.1.1.

### 7.2.2 Time with hypophosphatemia from baseline to day 35

The time with s-hypophosphatemia will be calculated as the actual number of days from the first day where s-phosphate < 2 mg/dL until the first day where s-phosphate ≥ 2 mg/dL. If the subject does not reach s-phosphate ≥ 2 mg/dL then it will be treated as censored at day 35. If a subject experiences more than one period with s-phosphate < 2 mg/dL, the longest period will be used in the analysis.

The time with hypophosphatemia from baseline to day 35 will be presented by a Kaplan-Meier plot. The treatment groups will be compared by a log-rank test. Only subjects who have one or more s-phosphate value(s) < 2 mg/dL will be included.

Plots including the Kaplan-Meier curves, log-rank test and median time with hypophosphatemia will be presented overall by treatment. All periods will be presented by subject in a swimmer plot.

### 7.2.3 Proportion of hypophosphatemia at day 35

The proportion of subjects with hypophosphatemia at day 35 will be analysed and presented like the primary endpoint using the CMH described in section 5.1.1. for observed cases only.

The number and percentage of subjects with hypophosphatemia will be summarised by treatment and listed by subject as described in section 7.1.1.

### 7.2.4 Absolute [Δ] and relative [%] changes in s-phosphate from baseline to day 1, 7, 8, 14, 21, and 35

The change in s-phosphate from baseline to day 1, 7, 8, 14, 21, and 35 will be analysed and presented using the MMRM described in section 5.1.1.

The change in s-phosphate will be summarised by treatment and visit, and mean plot of absolute change over time will be presented.

The percentage change in s-phosphate from baseline to day 1, 7, 8, 14, 21, and 35 will be analysed and presented using the MMRM described in section 5.1.1.

The percentage change in s-phosphate will be summarised by treatment and visit, and mean plot of percentage change over time will be presented.

### 7.2.5 Fractional phosphate urinary excretion at day 1, 7, 8, 14, 21, and 35

The fractional phosphate urinary excretion at day 1, 7, 8, 14, 21, and 35 including change from baseline will be summarised by treatment and visit. All data will be listed by subject.

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## 7.2.6 Change in iFGF23, cFGF23, vitamin D (25, 1.25, 24.25), PTH, and ionized calcium from baseline to day 1, 7, 8, 14, 21, and 35

The change in each of the following 7 endpoints

- iFGF23
- cFGF23
- vitamin D (25)
- vitamin D (1.25)
- vitamin D (24.25)
- PTH
- ionized calcium

from baseline to day 1, 7, 8, 14, 21, and 35 will be analysed using the MMRM described in section 5.1.1..

A summary of absolute values and change from baseline by treatment and visit, and mean plots of change over time will be presented for each endpoint. All data will be listed by subject.

## 7.2.7 Type and incidence of AEs

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 either occur after administration of randomised treatment or occur before and are worsened after randomised treatment. Related or possible related AEs are defined as Adverse Drug Reactions (ADRs).

Summary by system organ class (SOC) and preferred term (PT) indicating number and percentage of subjects and number of events will be presented for:

- TEAEs
- Treatment emergent serious adverse events (SAEs)
- TEAEs by severity (mild, moderate, severe)
- TEAEs by relationship (related, possible, unlikely, not related, unknown)

An overall summary table by treatment will present number of events, number of subjects, and proportion of subjects reporting Non-TEAEs, TEAEs, Treatment emergent SAEs, Fatal SAEs, ADRs, Suspected Unexpected Serious Adverse Reaction (SUSARs), TEAEs by severity, and TEAEs by outcome. Number of subjects who experience an ADR including SUSARs will be compared between treatment groups using Fisher's Exact test.

Non-treatment emergent SAEs for subjects who never received trial drug will be listed.

The following lists will be made for the safety analysis set:

- Non-treatment emergent AEs and SAEs
- TEAEs
- Treatment emergent SAEs
- ADRs
- AEs leading to dose reduction or withdrawal from treatment
- Fatal SAEs

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## 7.2.8 Serious or severe hypersensitivity reaction

The hypersensitivity reactions are defined by the SMQs but including four additional terms, see the protocol Appendix A.

The number of events, number of subjects, and proportion of subjects reporting serious or severe hypersensitivity reaction starting on or after the first dose of randomized treatment will be summarised by SMQ and PT. Serious or severe hypersensitivity reactions will be listed.

## 7.3 Analysis and Presentation of the Secondary Efficacy Endpoints

The secondary efficacy endpoints are

- Change in Hb per gram iron in dose of randomised treatment from baseline to day 1, 7, 8, 14, 21, and 35
- Change in s-ferritin from baseline to day 1, 7, 8, 14, 21, and 35
- Change in TSAT from baseline to day 1, 7, 8, 14, 21, and 35

### 7.3.1 Change in Hb per gram iron

The absolute change in Hb per gram iron in planned dose of randomised treatment from baseline to day 1, 7, 8, 14, 21, and 35 will be analysed and presented using the MMRM described in section 5.1.1. for ITT analysis set and FAS.

The absolute change in Hb per gram iron in actual dose of randomised treatment from baseline to day 1, 7, 8, 14, 21, and 35 will be analysed and presented using the MMRM described in section 5.1.1. for the PP analysis set.

The absolute values and change from baseline will be summarised by treatment and, and mean plot of change over time will be presented. All data will be listed by subject.

### 7.3.2 Change in s-ferritin

The absolute change in s-ferritin from baseline to day 1, 7, 8, 14, 21, and 35 will be analysed and presented using the MMRM described in section 5.1.1.

The absolute values and change from baseline will be summarised by treatment and visit, and mean plot of change over time will be presented. All data will be listed by subject.

### 7.3.3 Change in TSAT

The absolute change in TSAT from baseline to day 1, 7, 8, 14, 21, and 35 will be analysed and presented using the MMRM described in section 5.1.1.

The absolute values and change from baseline will be summarised by treatment and visit, and mean plot of change over time will be presented. All data will be listed by subject.

## 7.4 Analysis and Presentation of Other Safety Assessments

Other safety assessments are

- Vital signs and weight
- Electrocardiogram (ECG)
- Standard laboratory data
- Physical examination

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#### 7.4.1 Vital signs and weight

Vital signs, i.e. heart rate, and systolic and diastolic blood pressure, is assessed at baseline and for ferric carboxymaltose also at day 7. Vital signs will be summarised by treatment, visit and time point (before/during/5-15 minutes after infusion /20-40 minutes after infusion), including change from pre-infusion at the treatment visit. Weight is assessed at baseline and day 35 and will be summarised including change from baseline by treatment and visit. All data will be listed by subject.

#### 7.4.2 ECG

A standard 12 lead ECG is recorded. All ECGs will be evaluated as normal or abnormal, and if abnormal then also evaluated as clinical significant or not. At treatment visits, which is at baseline and for ferric carboxymaltose also at day 7, two ECGs are recorded; one before administration of the trial drug and one approximately 30 minutes after start of the dosing. Only one ECG is recorded at the other visits. The 3 categories for the standard 12 lead ECG will be summarised by treatment, visit and time point. Shift tables of ECG before and after treatment will be presented at the treatment visits. All data will be listed by subject.

#### 7.4.3 Laboratory data

Eligibility laboratory assessments are performed at screening. Safety laboratory data is assessed at baseline and day 1, 7, 8, 14, 21, and 35. Vitamin E is assessed at baseline.

The number and percentage of subjects and number of events will be presented by visit for subjects experiencing treatment emergent clinically significant laboratory values. In addition, laboratory data will be plotted using boxplots by treatment and visit.

Values outside normal ranges will be flagged. Laboratory reference ranges will be listed. All safety laboratory data will be listed by subject, including eligibility and exploratory laboratory assessments.

#### 7.4.4 Physical examination

A physical examination is performed at baseline and day 35 based upon the Investigator's judgement and might include Head-Eyes-Ear-Nose-Throat, Cardiovascular system, Respiratory system, Nervous system, Gastrointestinal system, Musculoskeletal system, Urogenital system, Dermatology system, and Others if required.

A summary table of physical examination will be presented by body system and visit. All data will be listed by subject.

### 7.5 Exploratory endpoints

The exploratory endpoints are the following:

- Change in biochemical bone/muscle markers:
  - Serum N-terminal Propeptide of Type I Collagen (PINP)
  - Carboxy-terminal Collagen Crosslinks (CTX)
  - Plasma alkaline phosphatase (bone specific)
  - Plasma alkaline phosphatase (total)
  - Creatine kinase
- from baseline to day 1, 7, 8, 14, 21, and 35
- Change in Hb from baseline to day 1, 7, 8, 14, 21, and 35

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- Change in fatigue symptoms from baseline to day 14 and 35 measured by the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale
- Change in QoL from baseline to day 14 and 35 measured by Short Form - 36 (SF-36) questionnaire
- Change in bone pain from baseline to day 14 and 35 measured on a Visual Analogue Scale (VAS) scale
- Change in muscle strength from baseline to day 14 and 35 measured by grip strength
- Change in
  - Upper limb proximal muscle function measured by the "1 kg arm lift" test
  - Lower limb proximal muscle function measured by the "30 sec chair stand" test
from baseline to day 14 and 35
- Change in
  - respiratory muscles strength measured by Maximal Inspiratory Pressure (MIP)
  - respiratory muscles strength measured by Maximal Expiratory Pressure (MEP)
from baseline to day 14 and 35

### 7.5.1 Change in biochemical bone/muscle markers

Change in Biochemical bone/muscle markers

- Serum N-terminal PINP
- CTx
- Plasma alkaline phosphatase (bone specific)
- Plasma alkaline phosphatase (total)
- Creatine kinase

from baseline to day 1, 7, 8, 14, 21, and 35 will be analysed and presented using the MMRM described in section 5.1.1.. A summary of absolute values and change from baseline by treatment and visit will be presented for each endpoint. All data will be listed by subject.

### 7.5.2 Change in Hb

The absolute change in Hb from baseline to day 1, 7, 8, 14, 21, and 35 will be analysed and presented using the MMRM described in section 5.1.1.

The absolute values and change from baseline will be summarised by treatment and, and mean plot of change over time will be presented. All data will be listed by subject.

### 7.5.3 Change in fatigue symptoms

The FACIT fatigue scale consists of 13 items ranging from 0 (not at all) to 4 (very much). All items, except items An5 and An7 are reversed scored from 4 to 0. The total score range is 0-52. A score of less than 30 indicates severe fatigue, and the higher the score, the better QoL. If more than 50 % of the items for a subject at a given visit are missing, the total score will not be calculated. If less than 50 % (6 out of 13) of the items are missing, the scores are prorated using the average of the other answers in the scale.

$$Total\ score = \frac{Sum\ of\ individual\ scores\ x\ 13}{Number\ of\ items\ answered}$$

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Change in fatigue symptoms from baseline to day 14 and 35 measured by the FACIT Fatigue Scale will be considered a continuous measure and will be analysed and presented using the MMRM described in section 5.1.1.

A summary of absolute values and change from baseline by treatment and visit will be presented. All data will be listed by subject.

#### 7.5.4 Change in QoL

The SF-36 survey consists of the following eight scales with a total of 35 items:

- General health (GH, based on 5 items)
- Physical function (PF, based on 10 items)
- Physical role limitations (RP, based on 4 items)
- Emotional role limitations (RE, based on 3 items)
- Social function (SF, based on 2 items)
- Bodily pain (BP, based on 2 items)
- Vitality (VT, based on 4 items)
- Mental health (MH, based on 5 items),

plus, a self-evaluated transition (SET) scale (1 item).

Ten of the 35 items should be reversed to ensure the highest number indicates best possible health. The 10 items are GH item 1, 11b, and 11d, SF item 6, BP item 7 and 8, VT item 9a and 9e, and MH item 9d and 9h (please refer to the SF-36 questionnaire for the numbering of items). GH item 1 and BP item 7 and 8 will be scored using recommended scoring (please refer to the SF-36 Users Guide, Appendix D). Note: Item 7 and 8 belongs to the same scale, but of different length. To obtain the same length, the first category in item 8, "Not at all" are split into two, by those who answers "None" in item 7 and those who answer "very mild" to "very severe" in item 7. The combination "Not at all" and "None" is then the best possible category with a raw score of 6.

The items within each of the eight scales are then summarized to achieve the Raw Scores. The Raw Scores are transformed in to a scale from 0 to 100 using the following formula:

Transformed scale score = ((Actual raw score-lowest possible raw score)) / (possible raw score range) x 100.

The transformed scale scores are then further transformed into a z-score by subtracting each of the eight scale's 2009 U.S. general population mean from the score and then divide by the given scales standard deviation.

Each of the z-scores can then be transformed into T-scores with mean 50 and SD 10, i.e. each z-score is multiplied with 10 and then 50 is added.

Furthermore, a Physical Component Summary (PCS) and a Mental Component Summary (MCS) are derived, both based on the eight z-scores. For deriving PCS each of the z-scores is multiplied by its respective physical factor score coefficient and then the eight products are summarized. Similar the MCS are calculated using the mental factor score coefficients. The two scores are transformed into T-scores by multiplying by 10 and then adding 50. Note: a PCS and a MCS score can be computed if at least seven scales have been scored, one of which being the PF and MH scale, respectively.

Change in the eight health domain T-scores, and PCS T-score and MCS T-score from baseline to day 14 and day 35 will be considered continuous measures and will be analysed and presented using the MMRM described in section 5.1.1.

A summary of absolute values and change from baseline by treatment and visit will be presented. All data will be listed by subject.

Missing items will be imputed, please refer to section 7.6 for details.

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### 7.5.5 Change in bone pain

Bone pain is measured on a Visual Analogue Scale (VAS) and recorded on a scale ranging from 0 to 100, where a higher score indicates greater pain intensity.

Change in bone pain from baseline to day 14 and day 35 will be considered continuous and will be analysed and presented using the MMRM described in section 5.1.1. A summary of absolute values and change from baseline by treatment and visit will be presented. All data will be listed by subject.

### 7.5.6 Change in muscle strength

Muscle strength is measured by grip strength in kg with Jamar hand dynamometer. Three readings for each hand are done and the best of the six readings is recorded. Change in muscle strength from baseline to day 14 and 35 is considered continuous and will be analysed and presented using the MMRM described in section 5.1.1. A summary of absolute values and change from baseline by treatment and visit will be presented. All data will be listed by subject.

### 7.5.7 Change in upper and lower limb proximal muscle function

Upper limb proximal muscle function is measured by the "1 kg arm lift" test, where the number of times the weight is lifted above the head in a 30 second period is recorded for each arm individually and the final score is the mean of the two measurements.

Lower limb proximal muscle function is measured by the "30 sec chair stand" test, where the number of times that the subject rises to a full stand from the seated position with arms folded within 30 s is recorded.

Change in

- Upper limb proximal muscle function
- Lower limb proximal muscle function

from baseline to day 14 and 35 is considered continuous and will be analysed and presented using the MMRM described in section 5.1.1. A summary of absolute values and change from baseline by treatment and visit will be presented. All data will be listed by subject.

### 7.5.8 Change in respiratory muscles strength

Maximal Inspiratory Pressure (MIP) reflects the strength of the diaphragm and other inspiratory muscles. Maximal Expiratory Pressure (MEP) reflects the strength of the abdominal muscles and other expiratory muscles. Both are measured in cmH<sub>2</sub>O as continuous variables by a Micro Respiratory Pressure Meter (MicroRPM).

Change in

- MIP
- MEP

from baseline to day 14 and 35 will be analysed and presented using the MMRM described in section 5.1.1.

A summary of absolute values and change from baseline by treatment and visit will be presented. All data will be listed by subject.

## 7.6 Handling of Missing Values

For the primary endpoint, the first post-baseline s-phosphate measurement is taken at day 1, hence, very few missing values are expected. If there are subject(s), for whom no post-baseline s-phosphate

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measurement(s) are available, these subjects will be set as having s-phosphate < 2 mg/dL in the primary analysis.

In the MMRM analyses subjects without post-baseline values will have change from baseline set to 0 at the first post-baseline visit.

Missing values for the SF-36 questionnaires will be handled using the Half-scale rule, i.e. a score will be calculated if at least 50 % of the items are answered by a subject at a given visit. The missing items will be imputed by the average score of the non-missing items. The PCS score can be computed if at least seven scales have been scored, one of which being the PF scale; similarly, the MCS score can be computed if at least seven scales have been scored, one of which being the MH scale.

Besides from this no imputation of missing values will be applied.

## 7.7 Multiplicity adjustments

These trials are two-armed with one primary endpoint, so no multiplicity exists. For the secondary endpoints, treatment differences, CIs and corresponding p-values are presented, but no adjustment for multiplicity will be done.

## 7.8 Sub-group and Centre Effects

No sub-group analyses are planned. The trials are multi centre trials, but no adjustment for centre effects is planned.

## 7.9 Interim Analysis

No interim analysis is planned.

## 7.10 Combined Analysis of P-Monofer-IDA-04 and P-Monofer-IDA-05

The two trials P-Monofer-IDA-04 and P-Monofer-IDA-05 is planned to run in parallel and the same dosing regimens are investigated.

Pooled analyses of primary and secondary safety and efficacy endpoints will be performed for the two trials.

The analyses will be performed similar to those specified for the individual trials, with the addition of trial in the models, i.e. the CMH method will be stratified by strata and trial and the MMRM will include the fixed, categorical effects of trial, treatment, strata, day, treatment-by-day interaction. Also, the overall incidence of TEAEs and ADRs will be compared between the treatment groups using Fisher's Exact test.

The CSRs will be finalised without the combined analyses, which will be done when both trials are finalised. The combined analysis will be included as an appendix to the CSRs.

## 8 Deviations from Protocol

- If very few subjects are present in one of the strata, similar analyses to the primary analysis will be presented as additional analyses, where two of the categories are grouped.

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- The wording “*the proportion of subjects with hypophosphatemia*” is used for a secondary endpoint where the intention was to evaluate on “*the incidence of hypophosphatemia*”.
- In the description of how time with hypophosphatemia from baseline to day 35 is presented it is stated “All periods will be tabulated”. This will be presented by a swimmer lane plot.
- In the description of combined analysis of P-Monofer-IDA-04 and P-Monofer-IDA-05 it is specified “*The analyses will be performed similar to those specified for the individual trials, with the addition of trial in the models, i.e. the strata in the Cochran-Mantel-Haenszel method will be a combination of baseline s-phosphate and trial*”. Here the strata to be used is type of underlying disease and screening s-phosphate level together with trial and not baseline s-phosphate together with trial as specified in the protocol.
- The secondary efficacy endpoint Change in Hb from baseline to day 1, 7, 8, 14, 21, and 35 will be evaluated per gram iron as described in section 7.3.1. in order to align with Hb data included in the label of another IV iron product (Ferumoxytol). Change in Hb will also be evaluated based on full iron dose as an exploratory endpoint.
- The exploratory endpoint Change in Pyridinoline in the urine from baseline to day 1, 7, 8, 14, 21, and 35 has been omitted since it was an exploratory endpoint with a limited value, which showed to be quite challenging to both site and subjects due to very specific requirements of the urine sample. Instead the focus will be on the bone marker CTx.

## 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). SF-36 will be scored using QualityMetric Health Outcome Scoring Software version 5.1.

## 10 Reference List

Not applicable.