

Trial ID: P-Monofer-IDA-05

Protocol Version: 3.0 (amendment 2)

Date of Document : 29 November 2017

CLINICAL TRIAL PROTOCOL

A randomized, open-label, comparative trial comparing the incidence of hypophosphatemia in relation to treatment with iron isomaltoside and ferric carboxymaltose in subjects with iron deficiency anaemia

Trial ID: P-Monofer-IDA-05

Sponsor: Pharmacosmos A/S, Rørvangsvej 30, DK-4300 Holbæk, Denmark

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INVESTIGATOR'S STATEMENT

The Principal Investigator agrees to conduct the trial as outlined in this protocol and in accordance with global/local regulations and current International Conference on Harmonization Good Clinical Practise (ICH-GCP) guidelines. Any modification to the protocol must be approved in writing by Pharmacosmos A/S, Competent Authorities, and the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) as may be required by applicable regulations.

The Principal Investigator agrees, by written consent to this protocol, to fully co-operate with monitoring and audit checks by allowing direct access to subject's records, including source data, by authorised individuals representing Pharmacosmos A/S or Competent Authorities.

Approved consent in writing by Principal Investigator:

Date: _____

Name in print: _____

Signature: _____

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PROTOCOL SUMMARY

Trial title

A randomized, open-label, comparative trial comparing the incidence of hypophosphatemia in relation to treatment with iron isomaltoside and ferric carboxymaltose in subjects with iron deficiency anaemia

Trial design

The trial is a randomized, open-label, comparative trial. Subjects with Iron Deficiency Anaemia (IDA) will be randomized 1:1 to one treatment course of one of the following treatments:

- Group A: iron isomaltoside 1000 (Monofer®, Pharmacosmos, Holbæk, Denmark, termed iron isomaltoside in the following), 1000 mg at baseline
- Group B: ferric carboxymaltose (Ferinject®/Injectafer®, Vifor Inc, Switzerland), 750 mg 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.

Phase of trial

The trial is a phase III trial.

Background

IDA is highly prevalent in subjects with gastrointestinal diseases and cancer, menstruating or pregnant women, and subjects who have undergone bariatric procedure. IDA can have a substantial medical and Quality of Life (QoL) burden on the subjects and the treatment of these subjects includes controlling the bleeding and replenishing lost iron.

Oral iron administration is used in the clinical practice primarily because of its convenience. However, oral iron may not be tolerated by all subjects and iron loss may exceed the capacity for iron absorption. Hence, there is a need of an alternative in subjects, who do not tolerate oral iron or who require rapid repletion of iron stores, and intravenous (IV) iron is being increasingly used in patients not responding to oral iron.

Existing IV iron complexes differ in relation to the compounds capability to induce unintended hypophosphatemia to a degree defined as medical significant (i.e. serum (*s*-) phosphate < 2 mg/dL as defined in the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0), and in the medical review of ferric carboxymaltose performed by the Food and Drug Administration (FDA) in the USA it is stated that ferric carboxymaltose is associated with clinical significant hypophosphatemia. The effect of iron isomaltoside on *s*-phosphate has therefore been evaluated in several trials, showing a low frequency of hypophosphatemia in iron isomaltoside treated subjects.

It seems as the frequency of hypophosphatemia is highest in gynaecology patients and frequencies up to 50-70 % have been reported for ferric carboxymaltose in gynaecology patients with heavy uterine bleeding.

This trial is planned to evaluate the effect of IV iron isomaltoside compared to IV ferric carboxymaltose on phosphate in subjects with IDA, and it is intended that 50 % of the recruited subjects are women with IDA due to gynaecological blood losses.

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Objectives

The primary objective of the trial is to compare the incidence of hypophosphatemia in subjects with IDA treated with iron isomaltoside or ferric carboxymaltose.

The secondary safety objective of the trial is 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) *s*-phosphate (absolute [Δ] and relative [%] changes)
- (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

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

In addition to the 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) QoL
- (4) Bone pain
- (5) Muscle strength

Endpoints

The primary endpoint is the incidence of hypophosphatemia (defined as *s*-phosphate < 2 mg/dL) at any time from baseline to day 35.

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 subjects with hypophosphatemia at day 35
- Absolute [Δ] and relative [%] changes in *s*-phosphate from baseline to 1, 7, 8, 14, 21, and 35
- Fractional phosphate urinary excretion at 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 1, 7, 8, 14, 21, and 35
- Type and incidence of AEs

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- 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 Appendix A.

In addition, physical examinations and measurements of vital signs, height, weight, electrocardiogram (ECG), and safety laboratory parameters will be measured as part of standard safety assessments.

The secondary efficacy endpoints are the following:

- Change in Hb, *s*-ferritin, and TSAT from baseline to day 1, 7, 8, 14, 21, and 35

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), *s*-alkaline phosphatase (bone specific and total), and creatine kinase) from baseline to day 1, 7, 8, 14, 21, and 35
- 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 (SF)-36 questionnaire
- Change in bone pain from baseline to day 14 and 35 measured on a Visual Analogue Scale (VAS)
- Change in muscle strength from baseline to day 14 and 35 measured by grip strength
- Change in upper and lower limb proximal muscle function from baseline to day 14 and 35 measured by the "1 kg arm lift" test and the "30 sec chair stand" test.
- Change in respiratory muscles strength from baseline to day 14 and 35 measured by Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP)

Safety assessments

The trial includes the following safety assessments:

- Measurements of *s*-phosphate (blood and urine), iFGF23, cFGF23, vitamin D (25, 1.25, 24.25), PTH, and ionized calcium
- AEs will be collected and evaluated for relatedness, severity, seriousness, and expectedness. They will be reported to authorities and followed-up according to international and local requirements
- Physical examinations, measurements of vital signs, ECG, height, weight, and safety laboratory parameters

Efficacy assessments

The trial includes the following efficacy assessments:

- Hb, *s*-ferritin, TSAT, and *s*-iron

Exploratory assessments

The exploratory assessments include the following:

- Measurement of serum N-terminal PINP, CTx, *s*-alkaline phosphatase (bone specific and total), and creatine kinase

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- FACIT Fatigue Scale
- SF-36 questionnaire
- Bone pain assessed by a VAS
- Grip strength test
- "1 kg arm lift" test and "30 sec chair stand" test
- MIP and MEP

Participating countries

An updated list of the participating countries and sites will be kept in the trial master file.

Trial duration and number of visits

For the individual subject, duration of the trial will be approximately 9 weeks (including a 28 days screening period) and each subject will attend 8 visits.

Subject population

Subjects, who fulfil the following eligibility criteria, will be included.

Inclusion criteria:

A subject will be eligible for inclusion in the trial if he/she fulfils the following criteria:

1. Men or women > 18 years having IDA caused by different aetiologies* such as abnormal uterine bleeding, gastrointestinal diseases, cancer, bariatric procedures (gastric bypass operations), and other conditions leading to significant blood loss
2. Hb ≤ 11 g/dL
3. Body weight > 50 kg
4. S-ferritin ≤ 100 ng/mL
5. Estimated Glomerular Filtration Rate (eGFR) ≥ 65 mL/min/1.73 m²
6. S-phosphate > 2.5 mg/dL
7. Documented history of intolerance or unresponsiveness to oral iron therapy** for at least one month*** prior to trial enrolment
8. Willingness to participate and signing the Informed Consent Form (ICF)

*The aetiology (also if unknown) for IDA should be documented in the medical history and verified in the source documents.

**The intolerance and non-response to oral iron treatment should be documented with signs and symptoms in the medical history and verified in the source document.

***There should be a documentation of intolerance or unresponsiveness to at least one month of prescribed oral iron therapy per investigator's judgment within the last 9 months and they would not be candidates for oral iron again.

Exclusion criteria:

A subject will not be eligible for inclusion in this trial if he/she fulfils any of the following criteria:

1. Acute bleeding > 500 mL within 72 hours
2. Anaemia predominantly caused by factors other than IDA according to Investigator's judgment

3. Hemochromatosis or other iron storage disorders
4. Known hypersensitivity reaction to any component of iron isomaltoside or ferric carboxymaltose
5. Previous serious hypersensitivity reactions to any IV iron compounds (seriousness criteria are defined in Section 12.2)
6. Treatment with IV iron within the last 30 days prior to screening
7. Treatment with erythropoietin or erythropoietin-stimulation agents, red blood cell transfusion, radiotherapy, and/or chemotherapy within the last 30 days prior to screening
8. Received an investigational drug within the last 30 days prior to screening
9. Planned surgical procedure within the trial period
10. Alanine Aminotransferase (ALAT) and/or Aspartate Aminotransferase (ASAT) > 3 times upper limit of normal (e.g. decompensated liver cirrhosis or active hepatitis)
11. Surgery under general anaesthesia within the last 30 days prior to screening
12. Any non-viral infection within the last 30 days prior to screening
13. Alcohol or drug abuse within the past 6 months
14. Untreated hyperparathyroidism
15. Kidney transplantation
16. Estimated life expectancy of < 6 months or, for cancer patients, an Eastern Cooperative Oncology Group (ECOG) performance status > 1
17. Conditions that interfere with the subject's ability to understand the requirements of the trial and/or presumable non-compliance
18. Any other laboratory abnormality, medical condition, or psychiatric disorders which, in the opinion of the Investigator, will put the subject's disease management at risk or may result in the subject being unable to comply with the trial requirements
19. Pregnant or nursing women. In order to avoid pregnancy, women of childbearing potential have to use adequate contraception (e.g. intrauterine devices, hormonal contraceptives, or double barrier method) during the whole trial period and 7 days after the last dosing

Trial treatment

The subjects will be dosed with either one treatment course of iron isomaltoside (group A) or one treatment course of ferric carboxymaltose (group B) as described below.

Group A: iron isomaltoside will be administered as a single IV infusion of 1000 mg at baseline diluted in 100 mL 0.9 % sodium chloride and given over approximately 20 minutes (50 mg iron/min, cumulative dose: 1000 mg).

Group B: ferric carboxymaltose will be administered as 750 mg infused over at least 15 minutes at baseline and day 7 (cumulative dose: 1500 mg).

No premedication (e.g. antihistamine or steroids) is allowed before administration of the trial drug. If the subject is in daily treatment for e.g. allergy or asthma this is not considered as "premedication" and may be continued.

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Sample size calculations

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 (based on chi-square test).

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

In addition to the efficacy and safety analyses performed for this trial alone, an efficacy and safety assessment will be performed for the P-Monofer-IDA-04 and P-Monofer-IDA-05 trials combined. This is briefly described in Section 15.6.

Statistical analyses

The primary endpoint, incidence of hypophosphatemia (defined as *s*-phosphate < 2 mg/dL) 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 estimation of the risk difference and the associated 95 % CI, adjusting for strata (type of underlying disease (women with IDA due to gynaecological blood losses; yes/no) and screening *s*-phosphate level (< or \geq 3.5 mg/dL)) using the Cochran-Mantel-Haenszel method.

As sensitivity, the treatment groups will be compared between the treatment groups by a logistic regression model with treatment and type of underlying disease as factors and baseline *s*-phosphate as covariate and by Fisher's exact tests.

All subjects in the safety analysis set will be included in the analysis. The first post-baseline phosphate measurement will be taken at day 1; hence, very few missing values are expected. If there are subject(s), for whom no post-baseline phosphate measurement(s) are available, these subjects will be set as having *s*-phosphate < 2 mg/dL in the primary analysis.

All the statistical analyses will be described in a statistical analysis plan.

Ethical aspects

The trial will follow International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines and the Helsinki Declaration, and all subjects will sign informed consent before inclusion.

The protocol will be submitted to relevant authorities (Institutional Review Board (IRB)/Independent Ethics Committee (IEC), Competent Authorities, and Data Protection Agencies) according to local regulatory requirements prior to trial initiation.

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LIST OF APPENDICES

Appendix A: Standardised MedDra query (SMQ) terms (including four additional terms) for definition of hypersensitivity events

Appendix B: Southampton protocol for adult grip strength measurement

Appendix C: Tests of upper and lower limb proximal muscle function

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1 ABBREVIATIONS AND DEFINITIONS OF TERMS

1.1 Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALAT	Alanine Aminotransferase
ASAT	Aspartate Aminotransferase
BMW	Biometrics and Medical Writing
cFGF23	C-terminal Fibroblast Growth Factor 23
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRA	Clinical Research Associate
CRO	Contract Research Organizations
CRP	C-Reactive Protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTX	Carboxy-terminal Collagen Crosslinks
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FDA	Food and Drug Administration
FGF23	Fibroblast Growth Factor 23
GCP	Good Clinical Practice
Hb	Haemoglobin
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonization-Good Clinical Practice
IDA	Iron Deficiency Anaemia
IEC	Independent Ethics Committee
iFGF23	Intact Fibroblast Growth Factor 23
IRB	Institutional Review Board
ITT	Intention to Treat
IV	Intravenous
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Maximal Expiratory Pressure
MIP	Maximal Inspiratory Pressure
MMRM	Mixed Models for Repeated Measures
NMR	Nuclear magnetic resonance
PI	Principal Investigator

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PINP	Propeptide of Type I Collagen
PP	Per Protocol
PTH	Parathyroid hormone
QoL	Quality of Life
RBC	Red Blood Cell
REML	Restricted Maximum Likelihood
s-	Serum
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SF-36	Short Form-36
SmPC	Summary of Product Characteristics
SMQ	Standardised Medical Dictionary for Regulatory Activities Query
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCT	Trial Core Team
TSAT	Transferrin Saturation
VAS	Visual Analogue Scale
WBC	White Blood Cells

1.2 Definition of Terms

Baseline values	The “baseline” values are the values measured at the baseline visit, before first administration of the trial drug. For variables/assessments not performed on the baseline visit, the baseline value is the value from the screening period measured closest to the baseline visit.
Completed subject	A subject, who is enrolled in the trial after signing informed consent, exposed to trial drug, and not withdrawn or lost to follow up during the trial.
Documented history	The subject's own description is adequate to be entered in the medical file as source. Thus, no medical files from the referring physician or other are necessary.
End of trial	The end of trial is the last subject last visit date.
Final subject visit	The final trial visit for a subject. No trial related procedure is performed after this visit.
Iron isomaltoside	Iron isomaltoside 1000 (Monofer®)
Subject withdrawal	Time point when the subject exits from the trial prior to the planned completion of all trial drug administrations or assessments.
Screening period	The time period from signed informed consent until inclusion or exclusion from the trial.

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2 INTRODUCTION

2.1 Background

Iron Deficiency Anaemia (IDA) is highly prevalent in subjects with gastrointestinal diseases such as inflammatory bowel diseases [Wilson *et al.*, 2004] and cancer [Aapro *et al.*, 2012], menstruating or pregnant women [WHO, 2008], and subjects who have undergone bariatric procedure [Muñoz *et al.*, 2009]. IDA can have a substantial medical and Quality of Life (QoL) burden on the subjects, and treatment of these subjects includes controlling the bleeding and replenishing lost iron.

Oral iron administration is used in the clinical practice primarily because of its convenience. However, oral iron may not be tolerated by all subjects and iron loss may exceed the capacity for iron absorption. Hence, there is a need of an alternative in subjects, who do not tolerate oral iron or who require rapid repletion of iron stores, and intravenous (IV) iron is being increasingly used in patients not responding to oral iron. Moreover, some international guidelines recommend IV iron as the preferred option in the treatment of IDA in circumstances where there is decreased transport capacity and a high iron demand, as it is more effective and better tolerated than oral iron [Dignass *et al.*, 2015; KDIGO guideline, 2012; Gasche *et al.*, 2007].

Existing IV iron complexes differ in relation to the compounds capability to induce unintended hypophosphatemia [Food and Drug Administration (FDA) Advisory Committee Briefing Document, 2008; Okada *et al.*, 1983; Schouten *et al.*, 2009a; Schouten *et al.*, 2009b; Van Wyck *et al.*, 2009; Wolf *et al.*, 2013] to a degree defined as medical significant (i.e. *s*-phosphate < 2 mg/dL as defined in the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0), and in the medical review of ferric carboxymaltose performed by the FDA in the USA it is stated that ferric carboxymaltose is associated with clinical significant hypophosphatemia [FDA, 2013].

Mild to moderate severe hypophosphatemia is usually asymptomatic, and major clinical sequelae usually occur only with severe hypophosphatemia. Severe hypophosphatemia is associated with various complications including fatigue [Liu & Jeng, 2004], seizures [De Oliveira Iglesias *et al.*, 2009], osmotic demyelination syndrome [Turnbull *et al.*, 2013], myocardial depression [O'Connor *et al.*, 1977], ventricular tachycardia [Ognibene *et al.*, 1994], proximal myopathy [Russell, 1994], respiratory muscle weakness [Gravelyn *et al.*, 1988], rhabdomyolysis [Singhal *et al.*, 1992], haemolytic anaemia [Poesen *et al.*, 2012], muscle weakness, and bone pain [Schubert & DeLuca, 2010].

The effect of iron isomaltoside on serum (*s*-) phosphate has been evaluated in several trials. The frequency of transient hypophosphatemia in iron isomaltoside treated subjects is low; 0-1.8 % in chronic kidney disease patients [Bhandari *et al.*, 2015; Gupta *et al.*, 2013; Kalra *et al.*, 2016], 0-10 % in inflammatory bowel disease patients [Reinisch *et al.*, 2013; Reinisch *et al.*, 2015; Dahlerup *et al.*, 2016], 0 % in cardiology patients [Johansson *et al.*, 2015], 5 % in women with post-partum [Holm *et al.*, 2017], and 8 % in cancer patients [Birgegård *et al.*, 2016].

It has been suggested that hypophosphatemia associated with parenteral iron could be mediated by Fibroblast Growth Factor 23 (FGF23) [Durham *et al.*, 2007; Imel *et al.*, 2011; Schouten *et al.*, 2009a; Schouten *et al.*, 2009b; Shimizu *et al.*, 2009; Wolf *et al.*, 2013] which is a phosphate regulating peptide hormone secreted by osteocytes. Although the mechanism is poorly

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understood, it has been suggested that FGF23 leads to a suppression of renal tubular phosphate reabsorption and 1 α -hydroxylation of vitamin D, leading to hypophosphatemia [Schouten *et al.*, 2009b].

It seems as the frequency of hypophosphatemia is highest in gynaecology patients and frequencies up to 50-70 % have been reported for ferric carboxymaltose in gynaecology patients with heavy uterine bleeding [van Wyck *et al.*, 2009].

This trial is planned to evaluate the effect of IV iron isomaltoside 1000 (Monofer[®], Pharmacosmos, Holbæk, Denmark, termed iron isomaltoside in the following) compared to IV ferric carboxymaltose (Ferinject[®]/Injectafer[®], Vifor Inc, Switzerland) on phosphate in subjects with IDA, and it is intended that 50 % of the recruited subjects are women with IDA due to gynaecological blood losses.

2.2 Iron Isomaltoside

Iron isomaltoside is a complex between iron and a carbohydrate moiety. The carbohydrate isomaltoside 1000 is a purely linear chemical structure as shown by ¹³C Nuclear Magnetic Resonance (NMR) of repeating α -(1-6) linked glucopyranose residues. Thus, it is structurally different from the branched dextran polysaccharides present in iron dextran. Isomaltoside 1000 consists predominantly of 3-5 glucose units and is prepared from oligomers used for prevention of dextran-induced anaphylactic reaction. These oligomers have been chemically modified to further reduce the potential for anaphylactic/anaphylactoid reaction. Thus, isomaltoside 1000 is not a dextran [Jahn *et al.*, 2011].

Iron isomaltoside has strongly bound iron within the iron isomaltoside formulation, which enables a controlled, slow release of bioavailable iron to the iron-binding proteins with only a little risk of free iron toxicity [Jahn *et al.*, 2011]. This allows flexible dosing, including high and rapid dosing.

Following IV administration, iron isomaltoside is rapidly taken up by the cells in the reticuloendothelial system, particularly in the liver and spleen. Due to its molecular weight it is not eliminated by the kidneys [Monofer[®] Investigator's Brochure, current version].

Iron isomaltoside is available as aqueous solution for injection containing 100 mg iron/ml with pH between 5.0 and 7.0.

2.3 Trial Rationale

Among the various formulations of parenteral iron available on the market, iron isomaltoside may allow flexibility in terms of high and rapid dosing. The use of parenteral iron, especially in high doses, may result in better compliance, fewer visits to the medical practitioner, and overall improvement in QoL. However, IV iron complexes differ in relation to the compounds capability to induce unintended hypophosphatemia and frequencies up to 70 % have been reported for ferric carboxymaltose in gynaecology patients. Thus, this trial is planned to evaluate the effect of IV iron isomaltoside compared to IV ferric carboxymaltose on phosphate in subjects with IDA, and it is intended that 50 % of the recruited subjects are women with IDA due to gynaecological blood losses.

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3 TRIAL DESIGN

The trial is a randomized, open-label, comparative trial. The trial duration for the individual subject will be approximately 9 weeks (including a 28 days screening period) and each subject will attend 8 visits. Subjects with IDA will be 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.

4 TRIAL OBJECTIVES

4.1 Primary Objectives

The primary objective of the trial is to compare the incidence of hypophosphatemia in subjects with IDA treated with iron isomaltoside or ferric carboxymaltose.

4.2 Secondary Safety Objectives

The secondary safety objective of the trial is 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) S-phosphate (absolute Δ and relative [%] changes)
- (5) Fractional phosphate urinary excretion
- (6) Intact FGF23 (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

4.3 Secondary Efficacy Objectives

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

4.4 Additional Objectives

In addition to the 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) QoL
- (4) Bone pain
- (5) Muscle strength

5 TRIAL ENDPOINTS

5.1 Primary Endpoint

The primary endpoint is the incidence of hypophosphatemia (defined as *s*-phosphate < 2 mg/dL) at any time from baseline to day 35.

5.2 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 subjects with 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 Appendix A.

In addition, physical examinations and measurements of vital signs, height, weight, electrocardiogram (ECG), and safety laboratory parameters will be measured as part of standard safety assessments.

5.3 Secondary Efficacy Endpoint

The secondary efficacy endpoints are the following:

- Change in Hb, *s*-ferritin, and TSAT from baseline to day 1, 7, 8, 14, 21, and 35

5.4 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), *s*-alkaline phosphatase (bone specific and total), and creatine kinase) from baseline to day 1, 7, 8, 14, 21, and 35
- Change in fatigue symptoms from baseline to day 14 and 35 measured by the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale

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- Change in QoL from baseline to day 14 and 35 measured by Short Form (SF)-36 questionnaire
- Change in bone pain from baseline to day 14 and 35 measured on a Visual Analogue Scale (VAS)
- Change in muscle strength from baseline to day 14 and 35 measured by grip strength
- Change in upper and lower limb proximal muscle function from baseline to day 14 and 35 measured by the "1 kg arm lift" test and the "30 sec chair stand" test.
- Change in respiratory muscles strength from baseline to day 14 and 35 measured by Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP)

6 TRIAL VISITS

6.1 Pre-screening (optional)

The Principal Investigator (PI) will have the option of pre-screening potential trial candidates if the subject's Hb value is unknown to the Investigator and Hb testing is not part of standard care. This should be done by using a HemoCue Hb test, which will give an indication of whether the inclusion criteria could be fulfilled. It is up to the Investigator to decide if the candidate should proceed to screening. If the candidates continue into a regular screening visit all screening procedures including informed consent should be done according to the protocol.

The candidates should sign a separate pre-screening consent form prior to the HemoCue test.

6.2 Trial Visits

The subjects will attend 8 visits.

A trial flowchart of the trial assessments performed at the visits is shown in Table 1.

Table 1: Trial flowchart

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
Informed consent	X							
Demographics	X							
In/exclusion criteria	X	X						
Eligibility lab tests ^a	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 ^b						X
Height ^b		X						
Weight		X ^b						X

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
Vital signs ^c		X		(X)				
Randomization		X						
ECG ^c		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
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 ^d or		X						
Treatment with ferric carboxymaltose ^d		X		X				
Adverse events		X	X	X	X	X	X	X
Final visit form ^e								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 Section 7.8 (vital signs) and Section 7.9 (ECG).

d. All trial assessments should be done before administration of the trial drug unless otherwise stated in Section 7.

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

6.3 Visit 1 (Screening)

Visit 1 (screening) will be conducted within 28 days prior to visit 2 (baseline). The following will be done:

- Subject is informed about the trial and signs the informed consent
- Collection of demographic information
- Inclusion and exclusion criteria checked
- Eligibility laboratory assessments

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6.4 Visit 2 (Baseline)

Visit 2 (baseline) will be conducted a maximum of 28 days after visit 1 (screening). The following will be assessed:

- Inclusion and exclusion criteria reviewed to confirm that no change has occurred since screening
- Pregnancy test, if applicable
- Recording of relevant medical history
- Recording of concomitant medication
- Physical examination (not performed later than the baseline visit)
- Measurement of height
- Measurement of weight
- Examination of vital signs
- Randomization
- ECG
- Assessment of fatigue by FACIT Fatigue Scale
- Assessment of QoL by SF-36 questionnaire
- Assessment of pain intensity by a VAS
- Assessment of grip strength by Jamar hand dynamometer
- Assessment of upper limb proximal muscle function by the "1 kg arm lift" test
- Assessment of lower limb proximal muscle function by the "30 sec chair stand" test
- Assessment of respiratory muscles strength by MIP and MEP
- Measurement of vitamin E
- Safety laboratory tests
- Efficacy laboratory tests
- Exploratory laboratory tests
- Spot urine sampling
- Treatment with iron isomaltoside (group A only)
- Treatment with ferric carboxymaltose (group B only)
- AE evaluation and recording

6.5 Visit 3, Visit 5, and Visit 7

The following will be assessed:

- Changes in concomitant medication and medical history (worsening of symptoms or diseases shall be recorded as AEs)
- ECG
- Safety laboratory tests
- Efficacy laboratory tests
- Exploratory laboratory tests

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- Spot urine sampling
- AE evaluation and recording

6.6 Visit 4

The following will be assessed:

- Changes in concomitant medication and medical history (worsening of symptoms or diseases shall be recorded as AEs)
- Examination of vital signs (group B only)
- ECG
- Safety laboratory tests
- Efficacy laboratory tests
- Exploratory laboratory tests
- Spot urine sampling
- Treatment with ferric carboxymaltose (group B only)
- AE evaluation and recording

6.7 Visit 6

The following will be assessed:

- Changes in concomitant medication and medical history (worsening of symptoms or diseases shall be recorded as AEs)
- ECG
- Assessment of fatigue by FACIT Fatigue Scale
- Assessment of QoL by SF-36 questionnaire
- Assessment of pain intensity by a VAS
- Assessment of grip strength by Jamar hand dynamometer
- Assessment of upper limb proximal muscle function by the "1 kg arm lift" test
- Assessment of lower limb proximal muscle function by the "30 sec chair stand" test
- Assessment of respiratory muscles strength by MIP and MEP
- Safety laboratory tests
- Efficacy laboratory tests
- Exploratory laboratory tests
- Spot urine sampling
- AE evaluation and recording

6.8 Visit 8

The following will be assessed:

- Changes in concomitant medication and medical history (worsening of symptoms or diseases shall be recorded as AEs)
- Physical examination

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- Measurement of weight
- ECG
- Assessment of fatigue by FACIT Fatigue Scale
- Assessment of QoL by SF-36 questionnaire
- Assessment of pain intensity by a VAS
- Assessment of grip strength by Jamar hand dynamometer
- Assessment of upper limb proximal muscle function by the "1 kg arm lift" test
- Assessment of lower limb proximal muscle function by the "30 sec chair stand" test
- Assessment of respiratory muscles strength by MIP and MEP
- Safety laboratory tests
- Efficacy laboratory tests
- Exploratory laboratory tests
- Spot urine sampling
- AE evaluation and recording
- Completing the final visit form

7 TRIAL ASSESSMENTS

7.1 Demographic and Baseline Assessments

Date of birth, gender, race, ethnicity, and smoking habits will be collected. A current smoker is defined as a subject who has been smoking within the last 6 months.

7.2 Pregnancy Test

A urine pregnancy test will be performed for all women of childbearing potential. The test will be handled and interpreted by the site personnel.

7.3 Relevant Medical History

Relevant medical history will be recorded. Changes in medical history will be recorded at the subsequent visits during the trial (worsening of symptoms or diseases shall be recorded as AEs). The following will be collected: disease and start and stop date. Except for underlying disorder causing IDA, start dates occurring > 12 months before the enrolment into the trial should be set as > 12 months.

7.4 Concomitant Medication

If the subject is receiving any concomitant medication it will be recorded at the baseline visit. Changes in concomitant medication will be recorded in the subsequent visits during the trial. The following will be collected: brand name, indication, route, dose, frequency, unit, and start and stop date. Start dates occurring > 12 months before the enrolment into the trial should be set as > 12 months.

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7.5 Physical Examination

A physical examination will be performed based upon the Investigator's judgement and may include the following:

- Head-Eyes-Ear-Nose-Throat
- Cardiovascular system
- Respiratory system
- Nervous system
- Gastrointestinal system
- Musculo-skeletal system
- Urogenital system
- Dermatology system
- Others, if required

7.6 Height

Height will be measured without shoes.

7.7 Weight

Weight will be measured.

7.8 Vital Signs

Heart rate and blood pressure will be measured at the following time points when a subject receives trial drug: approximately 0-10 minutes before infusion, during infusion, 5-15 minutes, and 20-40 minutes after the infusion has ended. If vital signs are measured more than once in the given time interval, the lowest measurement of diastolic blood pressure (including the attendant systolic blood pressure and heart rate) for the period should be noted in the electronic Case Report Form (eCRF).

7.9 Electrocardiogram

A standard 12 lead ECG will be recorded (including date, time, and signature). At baseline and other treatment visits, two ECGs will be recorded; one before administration of the trial drug and one approximately 30 minutes after start of the dosing. Only one ECG should be recorded at the follow-up visits.

The ECGs do not need to be evaluated by a cardiologist.

7.10 Functional Assessment of Chronic Illness Therapy Fatigue Scale

The FACIT Fatigue Scale is used to measure fatigue symptoms of the subjects [Cella *et al.*, 2005]. It is a self-administered questionnaire which will be filled in by the subject.

7.11 Short Form-36 Questionnaire

The SF-36 questionnaire is used to measure QoL. SF-36 is a 36 item questionnaire developed from the Medical Outcomes Study in the United States [Brazier *et al.*, 1992]. The SF-36 com-

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prises eight health scales, covering functional status, well-being, and overall evaluation of health. It is a self-administered questionnaire which will be filled in by the subject.

7.12 Bone Pain Measurement

Bone pain is measured as pain intensity on a VAS [Woodforde & Merskey, 1972]. It is a 100 mm length continuous scale anchored by two verbal descriptors, one for each symptom extreme; "no pain" (score of 0) and "worst imaginable pain" (score of 100). Thus, a higher score indicates greater pain intensity.

Based on the distribution of pain VAS scores in postsurgical patients (knee replacement, hysterectomy, or laparoscopic myomectomy), who described their postoperative pain intensity as none, mild, moderate, or severe, the following cut points on the pain VAS have been recommended: no pain (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75–100 mm) [Jensen *et al.*, 2003].

7.13 Muscle Strength

Muscle strength is measured by grip strength. Grip strength can be measured quantitatively using a hand dynamometer. The Jamar hand dynamometer (Lafayette Instrument Company, USA) will be used as this is the most widely cited in the literature and accepted as the gold standard. The standardized Southampton protocol for adult grip strength measurement will be followed [Roberts *et al.* 2011]. Details of the measurement can be found in Appendix B.

7.14 Upper and Lower Limb Proximal Muscle Function

The upper and lower limb proximal muscle function is measured by the "1 kg arm lift" test and the "30 sec chair stand" test as described in Agarwal and Kiely, 2006.

For the "1 kg arm lift" test, the number of times the weight is lifted above the head in a 30 sec period is recorded for each arm individually and the final score is the mean of the two measurements. For the "30 sec chair stand" test, the final test score is the number of times that the subject rises to a full stand from the seated position with arms folded within 30 sec. Both tests provide a numerical score on a continuous scale that is operator independent. Neither test exhibits a ceiling effect, as the upper limit of repetitions for each test is infinite. If the subjects have severe weakness and are unable to perform the tests at all, the score is 0 [Agarwal & Kiely, 2006]. Details of the measurement can be found in Appendix C.

7.15 Respiratory Muscles Strength

The measurements of MIP and MEP provide a non-invasive clinical method for evaluating the strength of respiratory muscles, and it is the most widely used test to assess muscle pressures [ATS/ERS statement, 2002]. The MIP reflects the strength of the diaphragm and other inspiratory muscles, while the MEP reflects the strength of the abdominal muscles and other expiratory muscles. MIP and MEP will be measured by MicroRPM (CareFusion Germany 234 GmbH, Hoechberg, Germany). Three tests should be performed for both MIP and MEP with the highest value from the three tests taken as the achieved result. Details of the measurement can be found in the following instruction video: <http://www.bd-horizon.com/micro/modules/rpm/index.html>.

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7.16 Laboratory Assessments

It is requested that the blood samples are drawn before administering the trial drug, and, if possible, that they are drawn at the same time of the day at all visits in order to reduce any diurnal fluctuation in the parameters.

Laboratory assessments will be performed at a central laboratory. A Laboratory Manual will be provided to each site in which all laboratory procedures will be described.

7.16.1 Eligibility Laboratory Assessments

The following eligibility laboratory assessments will be performed:

- Complete haematology set: Hb, leucocytes/White Blood Cells (WBC), erythrocytes/Red Blood Cells (RBC), haematocrit, platelets, neutrophil granulocytes, lymphocytes, monocytes, eosinophils, basophils, Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin Concentration (MCHC), and reticulocyte count
- Biochemistry:
 - S-ferritin
 - S-phosphate
 - Alanine Aminotransferase (ALAT) and Aspartate Aminotransferase (ASAT)
 - C-reactive Protein (CRP)
 - Estimated Glomerular Filtration Rate (eGFR)
 - PTH

7.16.2 Vitamin E

Vitamin E will be measured at baseline visit as part of the demographic data.

7.16.3 Safety Laboratory Assessments

The following safety laboratory assessments will be analysed:

- S-phosphate
- iFGF23 and cFGF23
- Vitamin D (25, 1.25, 24.25)
- PTH
- Ionized calcium
- Complete haematology set: Leucocytes/WBC, erythrocytes/RBC, haematocrit, platelets, neutrophil granulocytes, lymphocytes, monocytes, eosinophils, basophils, MCH, MCV, MCHC, and reticulocyte count
- Biochemistry:
 - S-sodium, s-potassium, s-calcium, s-urea, s-creatinine, s-albumin
 - S-bilirubin, ASAT, ALAT
 - CRP

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7.16.4 Efficacy Laboratory Assessments

The following efficacy laboratory parameters will be analysed:

- Hb
- S-ferritin
- TSAT (*s*-iron and transferrin will be collected to calculate the TSAT)

7.16.5 Exploratory Laboratory Assessments

The following exploratory laboratory assessments will be analysed:

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

7.16.6 Urine Assessments

A spot urine sampling will be collected in order to assess the level of fractional *s*-phosphate excretion.

7.17 Adverse Events

AEs will be collected and evaluated for relatedness to trial drug, seriousness, severity, and expectedness. They will be reported to the authorities and followed-up according to local requirements (described in Section 12).

8 TRIAL POPULATION

8.1 Number of Subjects

A minimum of 120 subjects will be recruited, and they will be randomized 1:1 to one treatment course of one of the following treatments:

- Group A: iron isomaltoside (60 subjects)
- Group B: ferric carboxymaltose (60 subjects)

The blocked randomization of subjects to treatment arms will be stratified in order to balance the type of underlying disease (women with IDA due to gynaecological blood losses; yes/no) and screening *s*-phosphate level (< or \geq 3.5 mg/dL).

The procedure for preparing the randomization list will be approved by the Global Trial Responsible Statistician before the randomization is performed.

8.2 Inclusion Criteria

A subject will be eligible for inclusion in the trial if he/she fulfils the following criteria:

1. Men or women > 18 years having IDA caused by different aetiologies* such as abnormal uterine bleeding, gastrointestinal diseases, cancer, bariatric procedures (gastric bypass operations), and other conditions leading to significant blood loss
2. Hb ≤ 11 g/dL

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3. Body weight > 50 kg
4. S-ferritin ≤ 100 ng/mL
5. eGFR ≥ 65 mL/min/1.73 m²
6. S-phosphate > 2.5 mg/dL
7. Documented history of intolerance or unresponsiveness to oral iron therapy** for at least one month*** prior to trial enrolment
8. Willingness to participate and signing the Informed Consent Form (ICF)

*The aetiology (also if unknown) for IDA should be documented in the medical history and verified in the source documents.

**The intolerance and non-response to oral iron treatment should be documented with sign and symptoms in the medical history and verified in the source document.

***There should be a documentation of intolerance or unresponsiveness to at least one month of prescribed oral iron therapy per investigator's judgment within the last 9 months and they would not be candidates for oral iron again.

8.3 Exclusion Criteria

A subject will not be eligible for inclusion in this trial if he/she fulfils any of the following criteria:

1. Acute bleeding > 500 mL within 72 hours
2. Anaemia predominantly caused by factors other than IDA according to Investigator's judgment
3. Hemochromatosis or other iron storage disorders
4. Known hypersensitivity reaction to any component of iron isomaltoside or ferric carboxymaltose
5. Previous serious hypersensitivity reactions to any IV iron compounds (seriousness criteria are defined in Section 12.2)
6. Treatment with IV iron within the last 30 days prior to screening
7. Treatment with erythropoietin or erythropoietin-stimulation agents, red blood cell transfusion, radiotherapy, and/or chemotherapy within the last 30 days prior to screening
8. Received an investigational drug within the last 30 days prior to screening
9. Planned surgical procedure within the trial period
10. ALAT and/or ASAT > 3 times upper limit of normal (e.g. decompensated liver cirrhosis or active hepatitis)
11. Surgery under general anaesthesia within the last 30 days prior to screening
12. Any non-viral infection within the last 30 days prior to screening
13. Alcohol or drug abuse within the past 6 months
14. Untreated hyperparathyroidism
15. Kidney transplantation
16. Estimated life expectancy of < 6 months or, for cancer patients, an Eastern Cooperative Oncology Group (ECOG) performance status > 1

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17. Conditions that interfere with the subject's ability to understand the requirements of the trial and/or presumable non-compliance
18. Any other laboratory abnormality, medical condition, or psychiatric disorders which, in the opinion of the Investigator, will put the subject's disease management at risk or may result in the subject being unable to comply with the trial requirements
19. Pregnant or nursing women. In order to avoid pregnancy, women of childbearing potential have to use adequate contraception (e.g. intrauterine devices, hormonal contraceptives, or double barrier method) during the whole trial period and 7 days after the last dosing

8.4 Subject Recruitment

Informed consent must be obtained from the subject before any trial related procedures are carried out.

In obtaining and documenting informed consent, the Investigator should comply with any applicable regulatory requirements, and should adhere to International Conference on Harmonization-Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki.

Before informed consent is obtained the subject should be allowed ample time and opportunity to read the subject information sheet, to enquire about details of the trial, and to decide whether or not to participate.

If the subject wishes to participate, the written ICF should be completed as appropriate and then signed and personally dated by the subject and the Investigator who conducted the informed consent discussions. The procedure for obtaining the informed consent must follow the local requirements and legislation.

9 SUBJECT COMPLETION AND WITHDRAWAL

9.1 Screen Failures

The PI will maintain a list of screening numbers and names of the subjects who have been screened at the site in order to allow for identification of records at a later date. The reasons for failure should be noted in the screening log of the site file and the final visit form.

9.2 Re-screening

Subjects may be re-screened three times at the discretion of the PI. Each subject re-screened must be re-consented and allocated a new subject number. All required screening assessments must be repeated in accordance with the protocol.

9.3 Subject Withdrawal

The subject has the right to withdraw from the trial at any time and for any reason without prejudice to his/her future medical care by the physician or at the institution. The PI can withdraw subjects from the trial in the following situations; treatment failure, safety reasons, and protocol violations.

The subject may also withdraw the consent if he/she does not wish to or is unable to continue in the trial. The Investigator will discuss with the subject the most appropriate way to withdraw in order to ensure the subject's health. If a subject withdraws from the trial, the Investi-

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gator will perform all final visit assessments, besides the scheduled trial assessments for that visit. Upon subject withdrawal, the Investigator will fill in the final visit form including the reason for withdrawal.

A subject who withdraws from the trial will not be re-enrolled or replaced with a new subject.

9.4 Subject Completion

When the subject has completed the trial, the Investigator will fill in the final visit form.

9.5 Treatment after the Trial

When the trial has ended or if the subject is withdrawn from the trial, the subject will be treated according to standard hospital practice.

9.6 Early Trial Termination

Pharmacosmos A/S reserves the right to temporarily suspend or prematurely discontinue the trial at any time for reasons including, but not limited to; safety or ethical issues, severe non-compliance, and insufficient subject enrolment. For multi-centre trials, this can occur at one or more sites. If Pharmacosmos A/S decides that such action is needed, Pharmacosmos A/S or its designee will discuss this with the PI including the reasons for taking such action. The PI also has the right to temporarily suspend or prematurely discontinue this trial for mutually agreed reason(s) with Pharmacosmos A/S.

Pharmacosmos A/S or its designee will promptly inform all other PIs and/or institutions conducting the trial if the trial is suspended or terminated due to safety reasons.

Pharmacosmos A/S or its designee will promptly inform the Competent Authorities of the suspension or termination of the trial and the reason(s) for the action. If required by applicable regulations, the PI must inform the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) promptly and provide the reason for the suspension or termination.

10 INVESTIGATIONAL PRODUCTS

10.1 Description of Investigational Products

Iron isomaltoside

Iron isomaltoside is a complex between iron and a carbohydrate moiety. The carbohydrate isomaltoside 1000 is a purely linear chemical structure as shown by ^{13}C NMR of repeating α -(1-6) linked glucopyranose residues. Thus, it is structurally different from the branched dextran polysaccharides present in iron dextran. Isomaltoside 1000 consists predominantly of 3-5 glucose units and is prepared from oligomers used for prevention of dextran-induced anaphylactic reaction. These oligomers have been chemically modified to further reduce the potential for anaphylactic/anaphylactoid reaction. Thus, isomaltoside 1000 is not a dextran [Jahn *et al.*, 2011].

Iron isomaltoside has strongly bound iron within the iron isomaltoside formulation, which enables a controlled, slow release of bioavailable iron to the iron-binding proteins with only a little risk of free iron toxicity [Jahn *et al.*, 2011]. This allows flexible dosing, including high dose and rapid dosing.

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Following IV administration, iron isomaltoside is rapidly taken up by the cells in the reticuloendothelial system, particularly in the liver and spleen. Due to its molecular weight, it is not eliminated by the kidneys [Monofer® Investigator's Brochure, current version].

Iron isomaltoside is available as aqueous solution for injection/infusion containing 100 mg iron/mL with pH between 5.0 and 7.0.

Ferric carboxymaltose

Ferric carboxymaltose is a colloidal iron (III) hydroxide in complex with carboxymaltose, a carbohydrate polymer that releases iron. It is an aqueous complex with the chemical name polynuclear iron (III) hydroxide 4(R)-(poly-(1→4)-O- α -D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. It has a relative molecular weight of approximately 150,000 Daltons [Injectafer® prescribing information (USA), 07/2013].

Ferric carboxymaltose is provided as a dark brown, sterile, aqueous, isotonic colloidal solution for IV injection. Each mL contains 50 mg iron as ferric carboxymaltose in water for injection. Ferric carboxymaltose is available in 15 mL single-use vials. Sodium hydroxide and/or hydrochloric acid may have been added to adjust the pH to 5.0-7.0. Ferric carboxymaltose will be administered as 750 mg infused over at least 15 minutes at baseline and day 7 (cumulative dose: 1500 mg), which is an approved treatment course [Injectafer® prescribing information (USA), 07/2013].

10.2 Dosage, Administration and Blinding of Trial Drug

The subjects will be randomized 1:1 to one treatment course of one of the following treatments:

- Group A, iron isomaltoside will be administered as a single IV infusion of 1000 mg diluted in 100 mL 0.9 % sodium chloride and given over approximately 20 minutes (50 mg iron/min) at baseline (cumulative dose: 1000 mg)
- Group B, ferric carboxymaltose will be administered as 750 mg infused over at least 15 minutes at baseline and day 7 (cumulative dose: 1500 mg)

No premedication (e.g. antihistamine or steroids) is allowed before administration of the trial drug. If the subject is in daily treatment for e.g. allergy or asthma this is not considered as "premedication" and may be continued.

The subjects must be observed for signs and symptoms of hypersensitivity during and after trial drug administration for at least 30 minutes and until clinically stable following completion of each administration.

Details of administration and storage of iron isomaltoside and ferric carboxymaltose are further described in the Drug Handling Plan.

10.3 Dose Rationale

In the present trial, subjects will be given a cumulative dose of 1000 mg iron isomaltoside administered as a single infusion. Justification for this single dose regime is found in recent safety data. Up to 31 December 2016, more than 1700 subjects have been treated with iron isomaltoside including bolus injections and high single dose infusions up to 2500 mg administered over 2 minutes for bolus injections and 15-60 minutes for infusions without a test dose. No safety concerns were found with these single dose levels.

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In this trial we have included single doses of 1000 mg iron isomaltoside in order to elucidate the safety and effect of high doses of iron isomaltoside since higher dosing would result in better compliance and increased convenience due to fewer visits necessary to make the subjects iron replete.

In the majority of the trials with iron isomaltoside, single dose infusions of up to 1000 mg have been administered over 15 minutes. There is no apparent indication that there are any specific safety concerns related to this speed of administration of iron isomaltoside. In the present trial, iron isomaltoside will be administered over 20 minutes.

Ferric carboxymaltose will be administered as 750 mg infused over at least 15 minutes at baseline and day 7 (cumulative dose: 1500 mg), which is an approved treatment course [Injectafer® prescribing information (USA), 07/2013].

10.4 Side Effects of Iron Isomaltoside

Side effects for iron isomaltoside are described in the Investigator's Brochure for iron isomaltoside (current version).

10.5 Side Effects of Ferric Carboxymaltose

Side effects for ferric carboxymaltose are described in Injectafer® prescribing information (USA), 07/2013.

10.6 Preparation, Handling, and Labelling

Pharmacosmos A/S or its designee will be responsible for preparation and packaging of all trial medication. No trial product will be used after its expiry date. The contents of the label will be in accordance with all applicable regulatory requirements.

Details of administration and storage of iron isomaltoside and ferric carboxymaltose are further described in the Drug Handling Plan.

10.7 Handling and Storage

The investigational product must be dispensed or administered according to procedures described herein. Only subjects enrolled in the trial may receive the investigational product, and it must be administered in accordance with all applicable regulatory requirements. Only authorised site staff may supply or administer the investigational product. All investigational products must be stored in a secure area with access limited to the authorised site staff and under physical conditions that are consistent with investigational product-specific requirements.

10.8 Product Accountability

The PI is responsible for investigational product accountability, reconciliation, and record maintenance throughout the course of the trial in accordance with all applicable regulatory requirements.

The responsible person(s) will document the amount of investigational products received from and returned to Pharmacosmos A/S or its designee, and the amount supplied and/or administered to subjects.

11 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

11.1 Permitted Medications

Throughout the trial, the subject may take any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 11.2. Any concomitant medications administered while the subject is participating in the trial must be recorded on the source document and transcribed into the concomitant medication form.

11.2 Prohibited Medications and Non-drug Therapies

No premedication (e.g. antihistamine or steroids) is allowed before administration of the trial drug. If the subject is in daily treatment for e.g. allergy or asthma this is not considered as "premedication" and may be continued.

The following medication and non-drug therapy are not allowed during the trial period since they could potentially have an impact on the endpoints:

- 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
- Erythropoietin or erythropoietin-stimulation agents
- Radiotherapy
- Chemotherapy

12 ADVERSE EVENTS

12.1 Definition of Adverse Events

An AE is defined in the ICH-GCP guideline as "any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment" (ICH E6:1.2). An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A clinically significant abnormal laboratory finding is also regarded as an AE if the effect is unfavourable for the subject. It is the responsibility of the Investigator to review the laboratory test results and determine whether an abnormal laboratory value is clinically significant. In general, a clinically significant laboratory value which suggests disease progression and/or requires active management is considered as an AE. Clinical significant efficacy laboratory parameters (including related parameters) are not to be recorded as AEs unless these are considered lack of efficacy or overdose.

Clinical significant findings in physical examinations and ECGs are to be recorded as medical history if they are observed at baseline. Otherwise they should be recorded as AEs.

Worsening of a pre-existing medical condition (e.g. cancer or diabetes) must also be recorded as an AE (e.g. if there is an increase in severity, frequency, duration of the condition or worsening of outcome). Pre-planned procedures and pre-existing medical conditions (planned or

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present at the time of signing the ICF) that have not worsened are not considered AEs. These are recorded on the medical history pages of the eCRF.

12.2 Definition of Serious Adverse Events

A Serious Adverse Event (SAE) is defined as an AE that

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalisation (a minimum of an overnight stay in a health care facility)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is a medically important event or reaction

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the subject or might require intervention to prevent one of the other outcomes listed in the definition above.

If the above interventions are performed as standard of care and not associated with an AE, the health issue for which the intervention is being performed will not be considered an SAE. If there is a complication as a result of the procedure and the complication meets at least 1 serious criterion, that complication would be reported as an SAE.

12.3 Definition of an Adverse Drug Reaction

An Adverse Drug Reaction (ADR) is an AE that is judged by the Investigator or Pharmacosmos A/S to be “related” or “possible related” to the trial drug (see classification of relatedness in Section 12.4).

If the ADR fulfils at least 1 of the criterion for an SAE, it is considered a Serious Adverse Reaction (SAR). If the SAR is not listed as an expected side effect for iron isomaltoside [Monofer® Investigator’s Brochure, current version] or for ferric carboxymaltose [Injectafer® prescribing information (USA), 07/2013], it is considered a Suspected Unexpected Serious Adverse Reaction (SUSAR).

It is the responsibility of Pharmacosmos A/S to evaluate the SARs for expectedness.

12.4 Collection of Adverse Events

The Investigator is responsible for ensuring that all AEs (as defined in Section 12.1) observed by the Investigator or reported by the subject are properly collected and recorded in the subject’s medical record as well as in the AE pages of the eCRF.

AEs/SAEs occurring before administration of the trial drug are considered as non-treatment emergent, and those occurring after administration of the trial drug are considered as treatment emergent. Non-treatment emergent AEs/SAEs which are worsened after treatment with trial drug will be assessed as treatment emergent.

Non-treated subjects: All SAEs will be reported in the eCRF from the time a subject has signed the ICF and until he/she exits the trial. Non-serious AEs occurring in subjects who are never treated with the trial drug will not be collected.

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Treated subjects: From the time a subject has signed the ICF and until he/she exits the trial, all AEs/SAEs will be reported in the eCRF.

If a subject is permanently withdrawn from the trial because of an AE, this information must be included in the final visit form.

An AE should be described in the following manner: The nature of the event will be described in precise, standard medical terminology (i.e. not necessarily the exact words used by the subject). If known, a specific diagnosis should be stated. Furthermore, the Investigator should describe an AE regarding seriousness (see Section 12.2), severity, relatedness, action taken, and outcome.

Severity

- Mild: The AE does not interfere in a significant manner with the subject's normal functioning level, but may be an annoyance
- Moderate: The AE produces some impairment of functioning but is not hazardous to health, but is uncomfortable and/or an embarrassment
- Severe: The AE produces significant impairment of functioning or incapacitation and is a hazard to the subject

Relatedness

- Related: The AE is related to the medicinal product
- Possible related: A causal relationship is conceivable and cannot be dismissed
- Unlikely related: The event is most likely related to an aetiology other than the medicinal product
- Not related: No relatedness to the medicinal product

The categories "related" and "possible related" will be classified as related AEs and the categories "unlikely related" and "not related" will be classified as unrelated AEs in the Clinical Study Report (CSR).

Outcome

- Recovered/resolved: Complete clinical recovery without any sequel attributable to the event as per Investigator's discretion
- Recovered/resolved with sequelae: Complete clinical recovery but with one or more sequels attributable to the event as per Investigator's discretion
- Recovering/resolving: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial
- Not recovered/not resolved: The subject's condition has not improved and the symptoms are unchanged
- Fatal
- Unknown: The subject's condition is unknown. This term should only be used when no other definition is possible e.g. the subject is lost to follow-up

For the purpose of medical management, all AEs and laboratory abnormalities that occur during the trial must be evaluated by the Investigator. Each of these will be followed to satisfactory clinical resolution. Insofar as possible, all AEs should be followed-up to determine the

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final outcome of the event. The Investigator must follow-up all subjects with SAEs until the event has subsided (or disappeared), the condition has stabilised, the event is otherwise explained, or the subject is lost to follow-up.

12.5 Reporting of SAEs

The Investigator must report all SAEs promptly and within **24 hours** to Drug Safety at Pharmacosmos A/S after obtaining knowledge of the event.

The Investigator should report the SAEs by filling out the SAE form and report to Pharmacosmos A/S either by e-mail at **pv@pharmacosmos.com** or **fax number +45 5948 6082**.

Contact details: Drug Safety, Pharmacosmos A/S
Roervangsgade 30, DK-4300 Holbaek, Denmark
Phone: + [REDACTED]
Fax: +45 5948 60 82
E-mail: pv@pharmacosmos.com

After the initial SAE report, the Investigator is required, proactively, to provide further information regarding the subject's condition. All follow-up information must be forwarded to Pharmacosmos A/S as it becomes available.

For all AEs with fatal outcome, autopsy reports (if available) and relevant medical reports should be reported to Pharmacosmos A/S, as described above.

SAEs occurring after trial termination must be reported if considered related to the trial treatment.

Pharmacosmos A/S will report SUSARs to the Competent Authorities within 7 calendar days for fatal and life threatening SUSARs and follow-up information within the next 8 calendar days. All other SUSARs are submitted as soon as possible within 15 calendar days and relevant follow-up information is subsequently communicated as soon as possible.

Pharmacosmos A/S will inform any SUSARs to all PI(s) within 15 calendar days by circulating the Council for International Organizations of Medical Sciences (CIOMS-I) form.

All SAEs including expected SARs will be reported by Pharmacosmos A/S to the Competent Authorities by the annually Development Safety Update Report.

In addition, 6-monthly safety reports will be prepared by Pharmacosmos A/S and submitted to the Investigators for information.

13 PREGNANCIES

Subjects who become pregnant during the trial should continue the trial but cannot receive more trial drug.

If a subject becomes pregnant during the trial, they will be required to inform the Investigator about the pregnancy, delivery, and the health of the infant until 1 month of age. The Investigator must report the pregnancy and follow-up within 14 calendar days of obtaining the information. Pregnancy complications must be recorded as an AE. If the infant has a congenital anomaly/birth defect, this must be reported and followed up as an SAE.

The site will send a copy of the pregnancy form to Pharmacosmos A/S within 1 working day to Drug Safety, contact details in Section 12.5.

14 OVERDOSE

Overdose may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as *s*-ferritin may assist in recognising iron accumulation. Supportive measures such as chelating agents can be used.

An overdose must be reported as an AE.

15 STATISTICAL ANALYSES

15.1 Hypotheses

The following hypotheses will be tested:

The incidence of hypophosphatemia is not different in the two treatment groups.

$H_0: \pi_{\text{iron isomaltoside}} - \pi_{\text{ferric carboxymaltose}} = 0$

against the alternative:

$H_A: \pi_{\text{iron isomaltoside}} - \pi_{\text{ferric carboxymaltose}} \neq 0$

where, $\pi_{\text{iron isomaltoside}}$ and $\pi_{\text{ferric carboxymaltose}}$ denote the incidence of hypophosphatemia.

The null hypothesis will be tested against the alternative by estimation of the risk difference using the Cochran-Mantel-Haenszel method.

15.2 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 this trial.

15.3 Data Analysis Sets

The following data analysis sets will be used in the analyses of the data:

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.

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Full Analysis Set (FAS): The FAS will consist of all randomized subjects, 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 Section 17.3.

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

15.4 Interim Analysis

No interim analysis will be performed.

15.5 Key Elements of the Analysis Plan

The statistical analyses will be described in detail in a statistical analyses plan.

15.5.1 Safety Analyses

15.5.1.1 Primary Analysis

The incidence of hypophosphatemia (defined as *s*-phosphate < 2 mg/dL) 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 estimation of the risk difference and the associated 95 % CI, adjusting for strata (type of underlying disease (women with IDA due to gynaecological blood losses; yes/no) and screening *s*-phosphate level (< or \geq 3.5 mg/dL)) using the Cochran-Mantel-Haenszel method.

As sensitivity, the treatment groups will be compared between the treatment groups by a logistic regression model with treatment and strata as factors and baseline *s*-phosphate as covariate and by Fisher's exact tests.

All subjects in the safety analysis set will be included in the analysis. The first post-baseline *s*-phosphate measurement will be taken at day 1; hence, very few missing values are expected. If there are subject(s), for whom no post-baseline *s*-phosphate measurement(s) are available, these subjects will be set as having *s*-phosphate < 2 mg/dL in the primary analysis.

15.5.1.2 Secondary Analyses

The incidence of *s*-phosphate < 1.0 mg/dL at any time from baseline to day 35 and the incidence of *s*-phosphate < 2 mg/dL at day 35 will be presented similar to the primary endpoint.

The time with hypophosphatemia from baseline to day 35 will be presented by a Kaplan-Meier plot, and compared between the two groups by a log-rank test. Only subjects who have one or more *s*-phosphate value(s) < 2 mg/dL will be included. 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 \geq 2 mg/dL. If a subject experiences more than one period with *s*-phosphate < 2 mg/dL, the longest period will be used in the analysis. All periods will be tabulated.

The absolute and percentage change in *s*-phosphate from baseline to day 1, 7, 8, 14, 21, and 35 will be analysed using a Restricted Maximum Likelihood (REML)-based Mixed Models for Repeated Measures (MMRM) approach. All subjects in the safety analysis set with post-

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baseline *s*-phosphate data will be included with their observed data. For subjects without post-baseline *s*-phosphate 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, week, treatment-by-week interaction, as well as the continuous, fixed covariates of baseline *s*-phosphate value and base-line *s*-phosphate-by-week interaction.

The fractional phosphate urinary excretion at day 1, 7, 8, 14, 21, and 35 will be tabulated.

The 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 will be analysed by a MMRM model similar to *s*-phosphate.

15.5.1.3 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) current version.

Treatment emergent AEs will be summary tabulated by body system and preferred term indicating number and percentage of subjects and number of events. Number of subjects who experience an ADR including SUSARs will be compared between treatment groups.

The following AE listings will be made as a minimum:

- The following list will be made for subjects who never received trial drug:
 - Non-treatment emergent SAEs
- The following lists will be made for the safety analysis set:
 - Non-treatment emergent AEs and SAEs
 - Treatment emergent AEs (non-serious and serious)
 - Treatment emergent SAEs
 - ADRs
 - AEs leading to dose reduction or withdrawal from treatment
 - Serious or severe hypersensitivity reactions
 - Fatal SAEs

The incidence of serious or severe hypersensitivity reaction starting on or after the first dose of randomized treatment will be tabulated. The hypersensitivity terms are defined as SMQ terms (including four additional terms) in Appendix A.

15.5.1.4 Additional Safety Analyses

Vital signs, ECG, and standard laboratory data will be presented by descriptive statistics. The incidence of treatment emergent potentially clinically significant laboratory and vital sign values will be tabulated.

Physical examination will be tabulated (by body system) as described for categorical data above.

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15.5.2 Efficacy Analyses

The change in Hb, *s*-ferritin, and TSAT from baseline to day 1, 7, 8, 14, 21, and 35 will be analysed by a MMRM model similar to *s*-phosphate. All subjects in the ITT analysis set will be included.

15.5.3 Exploratory Analyses

The following exploratory endpoints will be analysed similar with a MMRM model similar to *s*-phosphate:

- Change in biochemical bone/muscle markers (serum N-terminal PINP, CTx, *s*-alkaline phosphatase (bone specific and total), and creatine kinase) from baseline to day 1, 7, 8, 14, 21, and 35
- Change in fatigue symptoms from baseline to day 14 and 35 measured by the FACIT Fatigue Scale
- Change in QoL from baseline to day 14 and 35 measured by SF-36 questionnaire
- Change in bone pain from baseline to day 14 and 35 measured on a VAS
- Change in muscle strength from baseline to day 14 and 35 measured by grip strength
- Change in upper and lower limb proximal muscle function from baseline to day 14 and 35 measured by the "1 kg arm lift" test and the "30 sec chair stand" test
- Change in respiratory muscles strength from baseline to day 14 and 35 measured by MIP and MEP

15.6 Combined Analysis of P-Monofer-IDA-04 and P-Monofer-IDA-05

The two trials P-Monofer-IDA-04 and P-Monofer-IDA-05 will run in parallel. With $n = 60$ treated with iron isomaltoside and $n = 60$ treated with ferric carboxymaltose, each trial has more than 80% power to detect a difference in the incidence of hypophosphatemia, defined as *s*-phosphate < 2 mg/dL at any point from day 1 to day 35.

In P-Monofer-IDA-04 and P-Monofer-IDA-05 the same dosing regimens are investigated:

- 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)

Pooled analyses of 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 strata in the Cochran-Mantel-Haenszel method will be a combination of baseline *s*-phosphate and trial.

Using the assumptions of incidences of 15 % for iron isomaltoside and 40 % for ferric carboxymaltose, with $n = 120$ for iron isomaltoside 1000 mg and $n = 120$ for ferric carboxymaltose, there is 99 % power to detect this difference.

The assumption of the incidence of *s*-phosphate < 2 mg/dL for iron isomaltoside is based on the subgroup in the trial P-Monofer-IDA-01 receiving 1000 mg ($n = 29$). For this subgroup, no subject experienced *s*-phosphate < 1 mg/dL. For ferric carboxymaltose, there has been observed incidences of 9 % [Bager & Dahlerup, 2016].

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Using assumptions of incidences of 1 % for iron isomaltoside and 9 % for ferric carboxymaltose, with n = 120 for iron isomaltoside 1000 mg and n = 120 for ferric carboxymaltose, there is 82% power to detect this difference.

Also, the overall incidence of treatment emergent AEs and ADRs will be compared between the treatments.

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

16 DATA MANAGEMENT AND DATA COLLECTION

16.1 Definition of Source Data

Source data is defined as all information in original records or certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). Source data location list needs to be filled in and maintained by the Investigator during the trial.

16.2 Data Management

Data management will be outsourced. The data collection tool for this trial will be an eCRF, which is compliant with 21 CFR Part 11 regulations. Subject data necessary for analyses and reporting will be entered into a validated database or data system. Clinical data management will be performed in accordance with applicable standards and data cleaning procedures.

The site staff will be trained before they have access to the eCRF and an eCRF guideline will be available.

17 TRIAL MONITORING

17.1 Trial Monitoring

In accordance with applicable regulations and ICH-GCP guidelines, Pharmacosmos A/S or its designee will contact the site prior to the start of the trial to review with the site staff the protocol, trial requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing the data collection procedures, the discussion will also include identification, agreement, and documentation of data items for which the eCRF may serve as the source document.

Pharmacosmos A/S and or its designee will monitor the trial for protocol compliance verifying the following, but not limited to:

- Safety and rights of subjects are being protected
- Trial is conducted in accordance with the currently approved protocol and any other trial agreements, ICH-GCP guidelines, and all applicable regulatory requirements
- Data are authentic, accurate, and complete

Risk based monitoring will be used and is described further in the Global Monitoring Plan.

The PI agrees to allow the Clinical Research Associate (CRA) direct access to all relevant documents for the purpose of verification of available data.

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17.2 Quality Assurance

To ensure compliance with ICH-GCP guidelines and all applicable regulatory requirements, Pharmacosmos A/S or its designee may conduct a quality assurance audit following intimation and appointment. Regulatory agencies may also conduct a regulatory inspection of this trial. Such audits/inspections can occur at any time during or after completion of the trial.

17.3 Protocol Deviations

Deviations from the protocol will be registered as protocol deviations which will be classified as minor, major, or Good Clinical Practice (GCP) deviations.

The following will be assessed as major protocol deviation:

- Out of visit window at three visits
- 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

18 TRIAL ADMINISTRATION

Pharmacosmos A/S will be responsible for trial administration as described in this section.

A list of laboratories, Contract Research Organizations (CROs), and other vendors will be kept in the trial master file.

18.1 Trial Core Team, GCP Quality Steering Committee, and GCP Quality Board

A Trial Core Team (TCT) will be established for the trial consisting of the following Sponsor personnel:

- Chief Medical Officer
- Quality Assurance
- Global Trial Management
- Global Medical Monitoring
- Quality Control
- Regulatory
- Biometrics and Medical Writing (BMW)

The purpose of the TCT is to ensure high quality, regulatory compliance, scientific validity, and transparency in all activities of the trial via robust planning and timely action. Regular meeting will be held.

Issues which have a general impact on GCP will be escalated to the GCP Quality Steering Committee consisting of:

- Chief Medical Officer
- Quality Assurance
- Head of Clinical Trial Management

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- Head of Drug Safety
- Quality Control
- Regulatory
- BMW

Serious GCP breach and GCP related issues of broad impact to Pharmacosmos A/S could be escalated to the GCP Quality Board consisting of:

- Chief Medical Officer
- Quality and Regulatory Affairs
- Medical Affairs
- Chief Executive Officer

18.2 Direct Access

Direct access to all source data and documents will be mandatory for representatives from Pharmacosmos A/S, Contract Research Organizations, IRB/IEC, Competent Authorities, and other national authorities (e.g. Data Protection Agency) for the purpose of verification of available data.

If an audit or inspection occurs, the PI and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

18.3 Trial and Site Closure

Upon completion or premature discontinuation of the site or trial, the CRA will conduct site closure activities with the PI or site staff, as appropriate, in accordance with applicable regulations, ICH-GCP guidelines, and Pharmacosmos A/S or its designee's procedures.

18.4 Records Retention

Following closure of the trial, the PI must maintain all site trial records in a safe and secure location mutually agreeable to the PI, Pharmacosmos A/S, or its designee. The records must be maintained to allow easy and timely retrieval when needed (e.g. audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g. microfiche, scanned, and electronic); however, caution needs to be exercised before such action is taken. The PI must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the PI must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

Pharmacosmos A/S or its designee will inform the PI of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the trial, as dictated by any institutional requirements, local laws or regulations, or Pharmacosmos A/S or its designee standard procedures; otherwise the retention period will by default be 25 years.

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The PI must notify Pharmacosmos A/S or its designee of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility and transfer of ownership of the records if the PI leaves the site.

18.5 Provision of Trial Results and Information to Principal Investigators

When the CSR is completed, Pharmacosmos A/S or its designee will provide the PI with a summary of the trial results. The PI is encouraged to share the summary results with the subjects, as appropriate. In addition, the PI will be given reasonable access to review the relevant statistical tables, figures, and reports and will be able to review the results for the entire trial at a Pharmacosmos A/S site or other mutually agreeable location.

18.6 Finance and Insurance

All agreements between the PI and Pharmacosmos A/S or designee must be signed prior to screening of the first subject in the clinical trial. The agreement must clearly state the rights and obligations of the parties concerned and include a detailed financial settlement.

Every subject participating in the trial will be insured in accordance with the local legal requirements against trial related injuries to health, which may occur during the trial.

Excluded from this, however, are injuries to health and deteriorations of illnesses already in existence which would have occurred or continued to exist even if the subject had not taken part in the clinical trial.

The insurance cover is jeopardised if the subject fails to report immediately to the PI or responsible physician any injury to health, which might have resulted from participation in the clinical trial, or if the subject undergoes any other medical treatment without their consent before the clinical trial has been completely finished, insofar as the individual subject is concerned.

The subject insurance will be arranged by Pharmacosmos A/S on the basis of the final trial protocol.

19 ETHICAL CONSIDERATIONS

19.1 Regulatory and Ethical Considerations

Pharmacosmos A/S or its designee will obtain favourable opinion/approval to conduct the trial from the IRB/IEC, Competent Authorities, and the Data Protection Agency in accordance with the local requirements prior to initiating the trial.

The trial will be conducted in accordance with all applicable regulatory requirements. The trial will also be conducted in accordance with ICH-GCP guidelines, all applicable subject privacy requirements, and the guiding principles of the Declaration of Helsinki.

19.2 Changes to the Protocol

The clinical trial procedures may be changed, and if the changes are substantial, both the IRB/IEC and Competent Authorities, as applicable, must approve/acknowledge the changes before they can be implemented. All substantial changes must be documented by protocol amendments, if applicable.

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20 PUBLICATION PLAN

A CSR will be prepared by Pharmacosmos A/S or its designee and reviewed by Pharmacosmos A/S. The CSR or a summary of the CSR should be sent to the IRB/IEC and Competent Authorities according to local legislation.

No data from the clinical trial may be published, presented, or communicated, except to Competent Authorities, prior to the release of the CSR, unless approved by Pharmacosmos A/S in writing. The PIs agree not to discuss externally or publish any result from the trial without the possibility of Pharmacosmos A/S to give comments for up to 90 days after receipt of the manuscript.

The trial will be registered at Clinicaltrials.gov.

The results of the trial, positive as well as negative, will be published by the end of the trial.

If the results of the trial are to be published in a journal, the authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

20.1 Uploading of Data on Public Websites

The primary and secondary endpoints will be uploaded on ClinicalTrial.gov in according to national requirements.

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APPENDIX A

Standardised MedDra query (SMQ) terms (including four additional terms) for definition of hypersensitivity events

Group A: Narrow terms pertaining to hypersensitivity reactions

- Anaphylactic reaction
- Anaphylactic shock
- Anaphylactic transfusion reaction
- Anaphylactoid reaction
- Anaphylactoid shock
- Circulatory collapse
- First use syndrome
- Kounis syndrome
- Shock
- Type I hypersensitivity

Group B: Broad terms pertaining to respiratory reactions potentially related to hypersensitivity

- Acute respiratory failure
- Asthma
- Bronchial oedema
- Bronchospasm
- Cardio-respiratory distress
- Chest discomfort
- Choking
- Choking sensation
- Circumoral oedema
- Cough
- Cyanosis
- Dyspnoea
- Hyperventilation
- Laryngeal dyspnoea
- Laryngeal oedema
- Laryngospasm
- Laryngotracheal oedema
- Mouth swelling
- Nasal obstruction
- Oedema mouth

- Oropharyngeal spasm
- Oropharyngeal swelling
- Respiratory arrest
- Respiratory distress
- Respiratory failure
- Reversible airways obstruction
- Sensation of foreign body
- Sneezing
- Stridor
- Swollen tongue
- Tachypnoea
- Throat tightness
- Throat oedema
- Tracheal obstruction
- Tracheal oedema
- Upper airway obstruction
- Wheezing

Group C: Broad terms pertaining to skin reactions potentially related to hypersensitivity

- Allergic oedema
- Angioedema
- Erythema
- Eye oedema
- Eye pruritus
- Eye swelling
- Eyelid oedema
- Face oedema
- Flushing
- Generalised erythema
- Injection site urticaria
- Lip oedema
- Lip swelling
- Ocular hyperaemia
- Oedema
- Periorbital oedema
- Pruritus
- Pruritus allergic

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- Pruritus generalised
- Rash
- Rash erythematous
- Rash generalised
- Rash pruritic
- Skin swelling
- Swelling
- Swelling face
- Urticaria
- Urticaria papular

Group D: Broad terms pertaining to cardiovascular reaction potentially related to hypersensitivity

- Blood pressure decreased
- Blood pressure diastolic decreased
- Blood pressure systolic decreased
- Cardiac arrest
- Cardio-respiratory arrest
- Cardiovascular insufficiency
- Diastolic hypotension
- Hypotension

Group E: Additional terms defined by the Food and Drug Administration (FDA)

- Syncope
- Unresponsiveness
- Loss of consciousness
- Seizure

APPENDIX B

Southampton protocol for adult grip strength measurement (equipment: Model J00105 JAMAR Hydraulic Hand Dynamometer or similar model) [Roberts *et al.* 2011].

- (1) Sit the participant comfortably in a standard chair with legs, back support, and fixed arms. Use the same chair for every measurement.
- (2) Ask them to rest their forearms on the arms of the chair with their wrist just over the end of the arm of the chair—wrist in a neutral position, thumb facing upwards.
- (3) Demonstrate how to use the Jamar handgrip dynamometer to show that gripping very tightly registers the best score.
- (4) Start with the right hand.
- (5) Position the hand so that the thumb is round one side of the handle and the four fingers are around the other side. The instrument should feel comfortable in the hand. Alter the position of the handle if necessary.
- (6) The observer should rest the base of the dynamometer on the palm of their hand as the subject holds the dynamometer. The aim of this is to support the weight of the dynamometer (to negate the effect of gravity on peak strength), but care should be taken not to restrict its movement.
- (7) Encourage the participant to squeeze as long and as tightly as possible or until the needle/measurement stops rising/increasing. Once the needle/measurement stops rising/increasing the participant can be instructed to stop squeezing.
- (8) Read grip strength in kilograms from the outside dial and record the result to the nearest 1 kg on the data entry form.
- (9) Repeat measurement in the left hand.
- (10) Do two further measurements for each hand alternating sides to give three readings in total for each side.
- (11) The best of the six grip strength measurements is used in statistical analyses so as to encourage the subjects to get as high a score as possible.
- (12) Also record hand dominance, i.e. right, left or ambidextrous (people who can genuinely write with both hands).



Figure 1. Southampton protocol for adult grip strength measurement.

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APPENDIX C

Tests of upper and lower limb proximal muscle function [Agarwal and Kiely, 2006].

The subject sits in a chair holding a 1 kg weight with the shoulder adducted, the elbow in full flexion, and the forearm in supination (Figure 1). He/she is asked to lift the arm above the head until the elbow is fully extended, then to lower the arm back to the starting position, and then repeat the action at his/her own pace. This devised test has been called the "1 kg arm lift" test. It is important that the emphasis is not on achieving a maximum possible number of repetitions within the time, but instead that the test is performed at a comfortable pace according to the subject's own rhythm. The number of times the weight is lifted above the head in a 30 s period is recorded for each arm individually and the final score is the mean of the two measurements. When the test cannot be performed in one arm, for reasons other than the muscle disease in question, such as elbow or shoulder arthritis, the score from the contralateral arm alone is used.

Figure 1. Photograph demonstrating the "1 kg arm lift" test. The subject sits in a chair holding the 1 kg weight with the shoulder adducted, the elbow in full flexion, and the forearm in supination. He/she is asked to lift the arm above the head until the elbow is fully extended, then to drop the arm back to the starting position, and then repeat the action at his/her own pace for a 30 s period.

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The "30 s chair stand" test is a valid and reliable measure of proximal lower limb strength in older adults. The subject is asked to stand upright from a chair with their arms folded across the chest, then to sit down again and then repeat the action at his/her own pace over a 30 s period (Figure 2). Again it is important to emphasize that the subject does not need to achieve a maximum possible number of repetitions within the time allocated, but that the test is performed at a comfortable pace according to the subject's own rhythm. It is important that the same or a similar chair is used on each occasion, as the score may be influenced by the height of the chair. The final test score is the number of times that the subject rises to a full stand from the seated position with arms folded within 30 s.



Figure 2. Photograph demonstrating the "30 s chair stand" test. The subject is asked to stand upright from a chair with their arms folded across the chest, then to sit down again, and then repeat the action at his/her own pace for a 30 s period.