

Trial ID: P-Monofer-IDA-03

Protocol Version: 3.0 (amendment 2)

Date of Document : 14 June 2017

CLINICAL TRIAL PROTOCOL

A phase III, randomised, open-label, comparative safety and efficacy trial of intravenous iron isomaltoside (Monofer[®]) and iron sucrose in subjects with iron deficiency anaemia who are intolerant or unresponsive to oral iron therapy or in whom the haemoglobin measurement in Investigators' opinion were sufficiently low as to require rapid repletion of iron stores to minimize the risk of receiving a blood transfusion

Trial ID: P-Monofer-IDA-03

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: _____

PROTOCOL SUMMARY

Trial title

A phase III, randomised, open-label, comparative safety and efficacy trial of intravenous iron isomaltoside (Monofer[®]) and iron sucrose in subjects with iron deficiency anaemia who are intolerant or unresponsive to oral iron therapy or in whom the haemoglobin measurement in Investigators' opinion were sufficiently low as to require rapid repletion of iron stores to minimize the risk of receiving a blood transfusion

Trial design

The trial is a randomised, comparative, open-label trial. Subjects with iron deficiency anaemia (IDA) who are intolerant or unresponsive to oral iron therapy or in whom the screening haemoglobin (Hb) measurement in Investigators' opinion were sufficiently low as to require rapid repletion of iron stores to minimize the risk of receiving a blood transfusion will be randomised 2:1 to 1 of the following treatment groups:

- Group A: iron isomaltoside 1000 (Monofer[®], Pharmacosmos, Holbæk, Denmark, termed iron isomaltoside in the following)
- Group B: iron sucrose (Venofer[®])

Phase of trial

The trial is a phase III trial.

Background

IDA is highly prevalent in subjects with cancer and gastrointestinal diseases such as inflammatory bowel diseases, 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 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.

Iron sucrose is a widely used parenteral iron product and therefore this product has been chosen as comparator in this trial which is planned to evaluate the safety and efficacy of intravenous (IV) iron isomaltoside compared to IV iron sucrose in subjects with IDA who are intolerant or unresponsive to oral iron therapy or in whom the Hb measurement in the Investigators' opinion were sufficiently low as to require rapid repletion of iron stores to minimize the risk of receiving a blood transfusion.

Objectives

The primary safety objective of the trial is to evaluate the safety of IV iron isomaltoside compared to iron sucrose in subjects with IDA when oral iron preparations are ineffective or cannot be used or in whom the screening Hb measurement in Investigators' opinion were sufficiently low as to require rapid repletion of iron stores.

The primary efficacy objective of the trial is to evaluate and compare the effect of iron isomaltoside to iron sucrose in its ability to increase Hb in subjects with IDA when oral iron

preparations are ineffective or cannot be used or in whom the screening Hb measurement in Investigators' opinion were sufficiently low as to require rapid repletion of iron stores.

The secondary efficacy objective of the trial is to evaluate and compare the effect of iron isomaltoside to iron sucrose on:

- Other relevant iron related biochemical parameters
- Fatigue symptoms
- Pharmacoeconomics

Endpoints

The co-primary safety endpoint is serious or severe hypersensitivity reaction starting on or after the first dose of randomised 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.

The adverse events (AEs) will be adjudicated in a blinded fashion by an independent Clinical Endpoint Adjudication Committee (CEAC) (described in a separate adjudication charter). The specified definition of adjudicated endpoints will be given in the charter.

The secondary safety endpoints are the following:

- Composite cardiovascular AEs starting on or after the first dose of randomised treatment (i.e. treatment-emergent). The adjudicated composite AEs includes the following:
 - Death due to any cause
 - Non-fatal myocardial infarction
 - Non-fatal stroke
 - Unstable angina requiring hospitalization
 - Congestive heart failure requiring hospitalization or medical intervention
 - Arrhythmias
 - Hypertension
 - Hypotension

The AEs will be adjudicated in a blinded fashion by an independent CEAC (described in a separate adjudication charter). The specified definition of adjudicated endpoints is given in Appendix B.

- Time to first composite cardiovascular safety AE
- Serum (*s*-) phosphate < 2 mg/dL at any time from baseline to weeks 1, 2, 4, or 8

Physical examinations and measurements of vital signs, height, weight, and safety laboratory parameters will be measured as part of standard safety assessments. Furthermore, intensive electrocardiogram (ECG) monitoring for evaluation of QTc prolongations will be performed in 35 subjects.

The co-primary efficacy endpoint is change in Hb from baseline to week 8.

The secondary efficacy endpoints are the following:

- Hb increase of ≥ 2 g/dL from baseline to weeks 1, 2, 4, or 8
- Time to change in Hb ≥ 2 g/dL
- Hb level of > 12 g/dL at any time from week 1 to week 8
- Increase in Hb concentration ≥ 2 g/dL at any time from week 1 to week 8
- *S*-ferritin level of ≥ 100 ng/mL and transferrin saturation (TSAT) of 20-50 % at any time from week 1 to week 8
- Change in concentrations of Hb from baseline to weeks 1, 2, and 4
- Change in concentrations of *s*-ferritin, TSAT, and *s*-iron from baseline to weeks 1, 2, 4, and 8
- Change in fatigue symptoms from baseline to weeks 1, 2, and 8 measured by the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale
- Resources used by the subject (per visit) and health care staff (per administration) measured by the ISDR questionnaire and health care resource use questionnaire, respectively

Safety assessments

The trial includes the following safety assessments:

- 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. Events will be adjudicated in a blinded fashion by an independent CEAC (described in a separate adjudication charter)
- Intensive ECG monitoring for evaluation of QTc prolongations in 35 subjects
- Physical examinations, measurements of vital signs, height, weight, and safety laboratory parameters

Efficacy assessments

The trial includes the following efficacy assessments:

- Measurements of Hb, *s*-ferritin, TSAT, and *s*-iron
- FACIT Fatigue Scale
- ISDR questionnaire and health care resource use questionnaire

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 10-15 weeks and each subject will attend 6-12 visits (3 visits are conducted by telephone).

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
2. Subjects 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.
3. Subjects with:
 - a. Up to 1 month run-in phase indicating intolerance or lack of response to oral iron or
 - b. A documented history of intolerance to oral iron therapy to at least one month of ordinated oral iron therapy within 9 months** prior to trial enrolment or
 - c. Screening Hb measurement in Investigators' opinion was sufficiently low as to require rapid repletion of iron stores to minimize the risk of eventual blood transfusion***
4. Hb ≤ 11 g/dL
5. TSAT < 20 %
6. S-ferritin < 100 ng/mL
7. Willingness to participate and signing the informed consent form

*The aetiology for IDA should be documented in the medical history and verified in the source document.

**The intolerance to oral iron treatment within the last 9 months should be documented in the medical history and verified in the source document with signs and symptoms that lead to discontinuation of the oral iron therapy and precluded further use of oral iron therapy.

*** The Hb measurement that in Investigators' opinion was sufficiently low as to require rapid repletion of iron stores to minimize the risk of receiving a blood transfusion should be documented in the source document.

Additional inclusion criteria after the run-in period:

After the run-in period, subjects who fulfil the following additional eligibility criteria will be included:

1. Hb level ≤ 11 g/dL
2. S-ferritin ≤ 800 ng/mL
3. Lack of efficacy: Hb increase < 1 g/dL at visit R4 (i.e. inadequate response to oral iron) and compliance to oral iron (pill counts), which needs to be ≥ 67 %

Or

1. Hb level ≤ 11 g/dL
2. S-ferritin ≤ 800 ng/mL
3. Inability to tolerate oral iron, as per discretion of the Investigator

Exclusion criteria:

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

1. Anaemia predominantly caused by factors other than IDA according to Investigator's judgment
2. Hemochromatosis or other iron storage disorders
3. Known hypersensitivity reaction to any component of iron isomaltoside or iron sucrose
4. Previous serious hypersensitivity reactions to any IV iron compounds
5. Previously randomised in a clinical trial with iron isomaltoside
6. Received an investigational drug within 30 days of screening
7. During 10-day period prior to screening; has been treated with IV iron
8. Erythropoiesis stimulating agent (ESA) treatment within 30 days before the screening visit
9. During 30-day period prior to screening or during the trial period; has or will be treated with a red blood cell transfusion, radiotherapy, and/or chemotherapy
10. During 30-day period prior to screening or during the trial period; has or will require a surgical procedure that necessitated general anaesthesia
11. Alanine aminotransferase (ALAT) and/or aspartate aminotransferase (ASAT) > 3 times upper limit of normal (e.g. decompensated liver cirrhosis or active hepatitis)
12. Any non-viral infection
13. Required dialysis for treatment of CKD
14. Alcohol or drug abuse within the past 6 months
15. Estimated life expectancy of < 6 months or, for cancer patients, an Eastern Cooperative Oncology Group (ECOG) performance status > 1
16. 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
17. 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 iron isomaltoside (group A) or iron sucrose (group B) as described below.

In 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).

In group B, iron sucrose will be administered as 200 mg undiluted IV push injections over approximately 2-5 minutes and repeated according to standard practice or physician choice up to a maximum of five times (1000 mg) within the first two weeks starting at baseline. A cumulative dose of 1000 mg is recommended. The cumulative dose of iron sucrose should be specified and documented at baseline.

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.

Sample size calculations

The co-primary endpoints are treatment-emergent serious and/or severe non-serious hypersensitivity AEs and change in Hb from baseline to week 8.

Safety:

Data from previous trials conducted with iron isomaltoside suggests that the incidence of treatment-emergent serious and/or severe non-serious hypersensitivity AEs for an IDA population can be expected to be approximately 1 % (IBD-01/IBD-02/CIA-01/PP-01: $n = 3/341 = 0.9\%$, 95 % confidence interval (CI): 0.2 %; 2.5 %), and similar for iron sucrose (CKD-03: $n = 1/114 = 0.9\%$, 95 % CI: 0.0 %; 4.8 %). A common incidence of 1.5 % will be assumed for the current trial.

As these are relatively rare events, an incidence of 0 % for placebo is assumed. Iron isomaltoside should be at most 50 % worse than the difference between iron sucrose and placebo, corresponding to a maximum relative risk of 2 ($1.5\% / (1.5\% - 0\%)^2$).

This trial will primarily assess the risk of the test drug under investigation. Arguing back from a relative risk of 2 gives that the upper bound of the 95 % CI for the incidence of treatment-emergent serious and/or severe non-serious hypersensitivity AEs should be at most 3 % ($2 \times 1.5\%$) for the iron isomaltoside treatment group.

Efficacy:

IDA-301 was a double-blind, placebo-controlled trial designed to compare the safety and efficacy of 1000 mg IV ferumoxytol to placebo. In this trial, 608 subjects were treated with ferumoxytol and 200 received placebo. The change in Hb from baseline to week 5 was the primary efficacy endpoint for the European Union regulators, and one of the secondary endpoints for U.S. regulators. The mean change was 2.6 g/dL (standard deviation (SD): 1.5) for IV ferumoxytol and 0.1 g/dL (SD: 0.9) for placebo. The estimated treated effect of IV ferumoxytol (i.e. the difference between ferumoxytol and placebo) was estimated to be approximately 2.5 g/dL with a 95 % CI ranging from 2.3 to 2.7 g/dL. The point estimate will be used as estimate of the treatment effect. Preserving 80 % of this effect is believed to provide reasonable assurance that iron isomaltoside is efficacious. Hence, the non-inferiority margin is set to $(1-0.8) \times 2.5 \text{ g/dL} \sim 0.5 \text{ g/dL}$.

Power:

The significance level is set to 5 %. With $n = 1000$ in the iron isomaltoside treatment group, there is 88 % power for demonstrating that the upper bound of the 95 % CI of the incidence of treatment-emergent serious and/or severe non-serious hypersensitivity AEs is less than 3 %. And with $n = 500$ in the iron sucrose treatment group, assuming no difference between the treatment groups, and assuming a common SD = 1.5 g/dL, there is 100 % power for demonstrating non-inferiority of the change in Hb from baseline to week 8, using a non-inferiority margin of -0.5 g/dL.

This yields a total power for demonstrating both co-primary endpoints of 88 % in the trial.

The CKD-04 trial will run in parallel with this trial and the sample size is the same, yielding a total of 2000 subjects to be treated with iron isomaltoside and 1000 with iron sucrose. In addition to the efficacy and safety analyses performed for this trial alone, an efficacy and safety

assessment will be performed for the two trials combined. This is briefly described in Section 0.

Subjects will be stratified according to type of underlying disease (gastroenterology, gynaecology, oncology, and ‘other’) and baseline cardiovascular risk (history of myocardial infarction, stroke, or congestive heart failure, yes/no).

Statistical analyses

The co-primary safety endpoint will be analysed by constructing an exact two-sided 95 % CI of the incidence of treatment-emergent serious and/or severe non-serious hypersensitivity AEs in the iron isomaltoside treatment group. If the upper bound of the 95 % CI is <3 %, the safety objective has been met.

The co-primary efficacy endpoint will be analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. All subjects in the intention to treat (ITT) analysis set with post baseline Hb data will be included with their observed data. For subjects without post baseline Hb 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 iron sucrose), week, treatment-by-week interaction, strata, as well as the continuous, fixed covariates of baseline Hb value and baseline Hb-by-week interaction. An unstructured (co)variance structure will be used to model the within-subject errors. If, unexpectedly, this analysis fails to converge, the following structures will be applied, in the following order; first-order ante-dependence, heterogeneous compound symmetry, compound symmetry. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The primary comparisons will be the contrasts between iron isomaltoside and iron sucrose at week 8 based on the least squares means for the treatment-by-week interaction effect. The estimated mean difference based on this model will be reported with two-sided symmetric 95 % CI, and if the lower bound of the 95 % CI is > -0.5 g/dL, the efficacy objective has been met.

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: Adjudicated composite cardiovascular endpoints

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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
CEAC	Clinical Endpoint Adjudication Committee
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRA	Clinical Research Associate
CRP	C-Reactive Protein
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ESA	Erythropoiesis Stimulating Agent
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
Hb	Haemoglobin
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonization-Good Clinical Practice
IDA	Iron Deficiency Anaemia
IEC	Independent Ethics Committee
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
NMR	Nuclear magnetic resonance
PI	Principal Investigator
PP	Per Protocol
QoL	Quality of Life
RBC	Red Blood Cell
s-	Serum
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised Medical Dictionary for Regulatory Activities Query
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCT	Trial Core Team
TEAE	Treatment Emergent Adverse Event

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TSAT	Transferrin Saturation
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.
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.

2 INTRODUCTION

2.1 Background

Iron deficiency anaemia (IDA) is highly prevalent in subjects with cancer [Aapro *et al.*, 2012] and gastrointestinal diseases such as inflammatory bowel diseases [Wilson *et al.*, 2004], 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.

Iron sucrose (Venofer[®]) is a widely used parenteral iron products and therefore this product has been chosen as comparator in this trial which is planned to evaluate the safety and efficacy of intravenous (IV) iron isomaltoside 1000 (Monofer[®], Pharmacosmos, Holbæk, Denmark, termed iron isomaltoside in the following) compared to IV iron sucrose in subjects with IDA who are intolerant or unresponsive to oral iron therapy or in whom the haemoglobin (Hb) measurement in the Investigators' opinion were sufficiently low as to require rapid repletion of iron stores to minimize the risk of receiving a blood transfusion.

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 reticulo-endothelial 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.

Thus, this trial is planned to compare the safety and efficacy of iron isomaltoside with another parenteral iron preparation (iron sucrose) in subjects with IDA and who are intolerant or unresponsive to oral iron therapy or who need iron rapidly.

3 TRIAL DESIGN

The trial is a randomised, comparative, open-label trial. The trial duration for the individual subject will be approximately 10-15 weeks and each subject will attend a minimum of 6 visits.

Subjects who have not a documented intolerance of oral iron for at least 1 month within the last 9 months should have up to 1 month of run-in period of oral iron in order to document intolerance or lack of response to oral iron (see details in Section 6.3). Subjects enrolled in the run-in period will attend 1-4 additional visits (R1-R4). Visits R1-R3 are conducted by telephone.

The subject in group B may attend additional 2 treatment visits (TV1-TV2) if deemed necessary by the Investigator in order to achieve the cumulative dose of iron sucrose. The subjects will be randomised 2:1 to 1 of the following treatment groups:

- Group A: Iron isomaltoside (1000 mg infusion)
- Group B: Iron sucrose (200 mg push injection up to 5 times), a cumulative dose of 1000 mg is recommended

4 TRIAL OBJECTIVES

4.1 Safety Objectives

The primary safety objective of the trial is to evaluate the safety of IV iron isomaltoside compared to iron sucrose in subjects with IDA when oral iron preparations are ineffective or cannot be used or in whom the screening Hb measurement in Investigators' opinion were sufficiently low as to require rapid repletion of iron stores.

4.2 Efficacy Objectives

The primary efficacy objective of the trial is to evaluate and compare the effect of iron isomaltoside to iron sucrose in its ability to increase Hb in subjects with IDA when oral iron preparations are ineffective or cannot be used or in whom the screening Hb measurement in Investigators' opinion were sufficiently low as to require rapid repletion of iron stores.

The secondary efficacy objective of the trial is to evaluate and compare the effect of iron isomaltoside to iron sucrose on:

- Other relevant iron related biochemical parameters
- Fatigue symptoms
- Pharmacoeconomics

5 TRIAL ENDPOINTS

5.1 Primary Safety Endpoint

The co-primary safety endpoint is serious or severe hypersensitivity reaction starting on or after the first dose of randomised 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.

The adverse events (AEs) will be adjudicated in a blinded fashion by an independent Clinical Endpoint Adjudication Committee (CEAC) (described in a separate adjudication charter). The specified definition of adjudicated endpoints will be given in the charter.

5.2 Secondary Safety Endpoints

The secondary safety endpoints are the following:

- Composite cardiovascular AEs starting on or after the first dose of randomised treatment (i.e. treatment-emergent). The adjudicated composite AEs includes the following:
 - Death due to any cause
 - Non-fatal myocardial infarction
 - Non-fatal stroke
 - Unstable angina requiring hospitalization
 - Congestive heart failure requiring hospitalization or medical intervention
 - Arrhythmias
 - Hypertension
 - Hypotension

The AEs will be adjudicated in a blinded fashion by an independent CEAC (described in a separate adjudication charter). The specified definition of adjudicated endpoints is given in Appendix B.

- Time to first composite cardiovascular safety AE
- Serum (s-) phosphate < 2 mg/dL at any time from baseline to weeks 1, 2, 4, or 8

5.2.1 Additional Safety Analyses

Physical examinations and measurements of vital signs, height, weight, and safety laboratory parameters will be measured as part of standard safety assessments. Furthermore, intensive electrocardiogram (ECG) monitoring for evaluation of QTc prolongations will be performed in 35 subjects.

5.3 Primary Efficacy Endpoint

The co-primary efficacy endpoint is change in Hb from baseline to week 8.

5.4 Secondary Efficacy Endpoints

The secondary efficacy endpoints are the following:

- Hb increase of ≥ 2 g/dL from baseline to weeks 1, 2, 4, or 8
- Time to change in Hb ≥ 2 g/dL
- Hb level of > 12 g/dL at any time from week 1 to week 8
- Increase in Hb concentration ≥ 2 g/dL at any time from week 1 to week 8
- *S*-ferritin level of ≥ 100 ng/mL and transferrin saturation (TSAT) of 20-50 % at any time from week 1 to week 8
- Change in concentrations of Hb from baseline to weeks 1, 2, and 4
- Change in concentrations of *s*-ferritin, TSAT, and *s*-iron from baseline to weeks 1, 2, 4, and 8
- Change in fatigue symptoms from baseline to weeks 1, 2, and 8 measured by the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale
- Resources used by the subject (per visit) and health care staff (per administration) measured by the ISDR questionnaire and health care resource use questionnaire, respectively

6 TRIAL VISITS

6.1 Pre-screening (optional)

The Principal Investigator (PI) will have the option of pre-screening potential trial candidates if the candidate'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 a minimum of 6 visits.

Subjects who have not a documented intolerance of oral iron for at least 1 month within the last 9 months should have up to 1 month of run-in period of oral iron in order to document intolerance or lack of response to oral iron. Subjects enrolled in the run-in period will attend 1-4 additional visits (R1-R4). Visits R1-R3 are conducted by telephone.

The subject in group B may attend additional 2 treatment visits (TV1-TV2) if deemed necessary by the Investigator in order to achieve the cumulative dose of iron sucrose.

A trial flowchart of the trial assessments performed at the visits is shown in Table 1a (patients enrolled in the run-in period) and Table 1b (patients with documented intolerance of oral iron).

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Table 1a: Trial flowchart for patients enrolled in the run-in period

Visit	1 Screening	R1 ^f	R2 ^f	R3 ^f	R4 ^{fg}	2 Baseline	TV1 ^h	3	TV2 ^h	4	5	6 Final visit
Time (days)	-49	-42	-35	-28	Maximum -14	0	3	7	10	14	28	56
Visit window (days)	-	± 2	± 2	± 2	± 2	-	± 1	± 1	± 1	± 2	± 2	± 3
Informed consent	X											
Demographics	X											
In/exclusion criteria	X					X						
Eligibility lab tests	X				X							
Pregnancy test, if relevant						X						
Medical history, including history of myocardial infarction, stroke, or congestive heart failure						X		X		X	X	X
Concomitant medication						X		X		X	X	X
Physical examination						X ^a						X
Height ^a						X						
Weight						X ^a						X
Vital signs ^b						X	(X)	X	(X)	X	X	X
Oral iron (only patients included in the run-in period)		X	X	X								

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Visit	1 Screening	R1 ^f	R2 ^f	R3 ^f	R4 ^{fg}	2 Baseline	TV1 ^h	3	TV2 ^h	4	5	6 Final visit
Time (days)	-49	-42	-35	-28	Maximum -14	0	3	7	10	14	28	56
Visit window (days)	-	± 2	± 2	± 2	± 2	-	± 1	± 1	± 1	± 2	± 2	± 3
Compliance to oral iron			X	X	X							
Tolerance to oral iron			X	X	X							
Randomisation						X						
ECG ^{bc}						X	(X)	X	(X)	X	X	X
FACIT Fatigue Scale						X		X		X		X
ISDR questionnaire						X						
Health care resource use questionnaire						X						
Safety lab tests						X		X		X	X	X
Efficacy lab tests						X		X		X	X	X
Treatment with iron isomaltoside ^d or						X						
Treatment with iron sucrose ^d						X	(X)	(X)	(X)	(X)		
Adverse events						X	(X)	X	(X)	X	X	X
Final visit form ^e												X

a. Physical examination, height, and weight may be measured between the screening and baseline visit.

b. For details of the assessment, please see Section 7.8 (vital signs) and Section 7.9 (ECG).

c. An ECG will be taken for all subjects. In addition, intensive ECG monitoring for evaluation of QTc prolongations will be performed in 35 subjects.

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.

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- f. Subjects who do not have a documented intolerance of oral iron for at least 1 month within the last 9 months or had a screening Hb measurement which in Investigators' opinion was sufficiently low as to require rapid repletion of iron stores to minimize the risk of eventual blood transfusion should have up to 1 month of run-in period of oral iron in order to document intolerance or lack of response to oral iron. Subjects enrolled in the run-in period will have 1-4 additional visits (R1-R4). Visits R1-R3 are conducted by telephone.
- g. If a subject has been withdrawn during the run-in period due to intolerance, the subject may attend visit R4 before day -14.
- h. Subjects in group B may attend up to 2 additional treatment visits (TV1-TV2). The TV visits are optional treatment visit for dosing with iron sucrose, if in the opinion of the Investigator required in order to achieve the cumulative dose of iron sucrose.

Table 1b: Trial flowchart for patients with documented intolerance of oral iron

Visit	1 Screening	2 Baseline	TV1 ^f	3	TV2 ^f	4	5	6 Final visit
Time (days)	Maximum -14	0	3	7	10	14	28	56
Visit window (days)	-	-	± 1	± 1	± 1	± 2	± 2	± 3
Informed consent	X							
Demographics	X							
In/exclusion criteria	X	X						
Eligibility lab tests	X							
Pregnancy test, if relevant		X						
Medical history, including history of myocardial infarction, stroke, or congestive heart failure		X		X		X	X	X
Concomitant medication		X		X		X	X	X
Physical examination		X ^a						X

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Visit	1 Screening	2 Baseline	TV1 ^f	3	TV2 ^f	4	5	6 Final visit
Time (days)	Maximum -14	0	3	7	10	14	28	56
Visit window (days)	-	-	± 1	± 1	± 1	± 2	± 2	± 3
Height ^a		X						
Weight		X ^a						X
Vital signs ^b		X	(X)	X	(X)	X	X	X
Randomisation		X						
ECG ^{bc}		X	(X)	X	(X)	X	X	X
FACIT Fatigue Scale		X		X		X		X
ISDR questionnaire		X						
Health care resource use questionnaire		X						
Safety lab tests		X		X		X	X	X
Efficacy lab tests		X		X		X	X	X
Treatment with iron isomaltoside ^d or		X						
Treatment with iron sucrose ^d		X	(X)	(X)	(X)	(X)		
Adverse events		X	(X)	X	(X)	X	X	X
Final visit form ^e								X

a. Physical examination, height, and weight may be measured between the screening and baseline visit.

b. For details of the assessment, please see Section 7.8 (vital signs) and Section 7.9 (ECG).

c. An ECG will be taken for all subjects. In addition, intensive ECG monitoring for evaluation of QTc prolongations will be performed in 35 subjects.

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.

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- f. Subjects in group B may attend up to 2 additional treatment visits (TV1-TV2). The TV visits are optional treatment visit for dosing with iron sucrose, if in the opinion of the Investigator required in order to achieve the cumulative dose of iron sucrose.

6.3 Run-in Period

Subjects who do not have a documented history of intolerance of oral iron for at least 1 month within the last 9 months should have a run-in period. In the run-in period, the subject will receive oral iron for up to 1 month in order to document intolerance or lack of response to oral iron. If the subject fulfils the inclusion/exclusion criteria he/she will be enrolled into the run-in period after a telephone confirmation call at day -42 (visit R1). In the run-in period, the subject has to take 325 mg oral iron sulphate (Ferrous Sulphate 325 mg) three times daily. The oral iron sulphate will be provided by Pharmacosmos A/S. The subjects will have a telephone call at day -35 (visit R2) and day -28 (visit R3) in order to assess compliance (via pill counts) and tolerance of oral iron. At day -14, the subjects will have a visit (visit R4) in order to assess compliance (via pill counts) and tolerance of oral iron, and a blood sample will be drawn in order to assess the Hb and s-ferritin levels.

Subjects who report severe diarrhoea, constipation, vomiting, or abdominal pain with oral iron at the telephone calls after 7 and 14 days of oral iron treatment (day -35 and day -28) or before are withdrawn from the run-in and may continue directly to visit R4 (day -14). If all inclusion/exclusion criteria are fulfilled at visit R4 (day-14) the subject may be enrolled in the trial. Subjects who report other side effects are to reduce the oral iron dose to 325 mg once daily for the remaining run-in period.

If the subject experience severe diarrhoea, constipation, vomiting, or abdominal pain at any time during the run-in period, he/she should contact the site. The subjects are withdrawn from the run-in and if all other inclusion/exclusion criteria are fulfilled at visit R4 (day-14) the subject may be enrolled in the trial.

After 28-30 days treatment with oral iron, the subject will attend visit R4 (day -14). If a subject has been withdrawn during the run-in period due to intolerance, the subject may attend visit R4 before day -14. Subjects who respond adequately to oral iron during run-in (Hb increase ≥ 1 g/dL) are excluded from the trial. Subjects who have a Hb level ≤ 11 g/dL and s-ferritin ≤ 800 ng/mL after the run-in period and either an inadequate response to oral iron (i.e. Hb increase < 1 g/dL at visit R4 and a compliance of ≥ 67 % to oral iron) or an inability to tolerate oral iron, as per discretion of the Investigator, are enrolled into the trial if all inclusion/exclusion criteria are fulfilled. The following will be assessed during and/or after the run-in period:

- Compliance to oral iron (pill counts), which needs to be ≥ 67 %
- Severe intolerance defined as severe diarrhoea, constipation, vomiting, or abdominal pain
- Response to oral iron (Hb and ferritin)

6.4 Visit 1 (Screening)

The following will be assessed:

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

6.5 Visit 2 (Baseline)

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, including history of myocardial infarction, stroke, or congestive heart failure
- Recording of concomitant medication
- Physical examination (not performed later than the baseline visit)
- Measurement of height
- Measurement of weight
- Examination of vital signs
- Randomisation
- ECG (intensive ECG monitoring for evaluation of QTc prolongations will be performed in 35 subjects treated with iron isomaltoside)
- Assessment of fatigue by FACIT Fatigue Scale
- Assessment of pharmacoeconomics by the ISDR questionnaire and health care resource use questionnaire
- Safety laboratory tests
- Efficacy laboratory tests
- Treatment with iron isomaltoside (group A only)
- Treatment with iron sucrose (group B only)
- AE evaluation and recording

6.6 Visit 3

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
- ECG
- Assessment of fatigue by FACIT Fatigue Scale
- Safety laboratory tests
- Efficacy laboratory tests
- Treatment with iron sucrose (group B only), if required
- AE evaluation and recording

6.7 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
- ECG
- Assessment of fatigue by FACIT Fatigue Scale
- Safety laboratory tests
- Efficacy laboratory tests
- Treatment with iron sucrose (group B only), if required
- AE evaluation and recording

6.8 Visit 5

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
- ECG
- Safety laboratory tests
- Efficacy laboratory tests
- AE evaluation and recording

6.9 Visit 6 (final visit)

The following will be assessed:

- Changes in concomitant medication and medical history (worsening of symptoms or diseases shall be recorded as AEs)
- Physical examination
- Measurement of weight
- Examination of vital signs
- ECG
- Assessment of fatigue by FACIT Fatigue Scale
- Safety laboratory tests
- Efficacy laboratory tests
- AE evaluation and recording
- Completing the final visit form

6.10 Optional Treatment Visit (TV1-TV2)

Subjects in group B may attend up to 2 additional treatment visits (TV1-TV2). The TV visits are optional treatment visit for dosing with iron sucrose, if in the opinion of the Investigator required in order to achieve the cumulative dose of iron sucrose. The following will be assessed:

- Examination of vital signs

- ECG
- Treatment with iron sucrose
- AE evaluation and recording

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 including history of myocardial infarction, stroke, or congestive heart failure. Intolerance and non-response to oral iron treatment as well as the underlying disorder causing IDA should be documented in the medical history. 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: generic name, indication, dose, and start and stop date. Start dates occurring > 12 months before the enrolment into the trial should be set as > 12 months.

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 (HEENT)
- 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.

7.7 Weight

Weight will be measured.

7.8 Vital Signs

Heart rate and blood pressure will be measured.

At the treatment visits, heart rate and blood pressure will be measured at the following time points:

- For subjects receiving an infusion of iron isomaltoside: approximately 0-10 minutes before infusion, during infusion, 5-15 minutes, and 20-40 minutes after the infusion has ended
- For subjects receiving a push injections of iron sucrose: approximately 0-10 minutes before injection, 5-15 minutes, and 20-40 minutes after the injection has ended

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. In addition, intensive ECG monitoring for evaluation of QTc prolongations as well as pharmacokinetic assessments (described in Section 7.12.4) will be performed at baseline in 35 consecutive subjects in relation to treatment with iron isomaltoside at selected sites. The intensive ECGs will be described in a specific procedure description (sub-protocol). The intensive ECGs will be evaluated centrally 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 out by the subject.

7.11 Pharmacoeconomics

The ISDR questionnaire will be used to measure the resources used to receive treatment at one visit by the subject. Questions 5 and 10 of the questionnaire have been rephrased so that the questionnaire only includes resources used on preparation for the visit, travel time, and receiving the trial drug. Thus, resources used on other trial activities are not included. The questionnaire is based on independent research funded by the National Institute for Health Research under the Program Grants for Applied Research program (RP-PG-1210-12016).

The health care resource use questionnaire will include questions regarding time used by the health care staff during administration of the trial drug and the administration time (including the observational time). The questions will include the following:

- What is your profession (nurse, doctor, etc.)?

- How much time did you use on administration of the trial drug including preparing for the administration, administration time, and observation time?

7.12 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.

7.12.1 Eligibility Laboratory Assessments

The following eligibility laboratory assessments will be performed at screening:

- 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
 - TSAT
 - Alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT)
 - C-reactive protein (CRP)

The following eligibility laboratory assessments will be performed at visit R4:

- Hb
- *S*-ferritin

7.12.2 Safety Laboratory Assessments

The following safety laboratory assessments will be analysed:

- 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*-phosphate, *s*-urea, *s*-creatinine, *s*-albumin
 - *S*-bilirubin, ASAT, ALAT
 - CRP

7.12.3 Efficacy Laboratory Assessments

The following efficacy laboratory parameters will be analysed:

- Hb
- *S*-ferritin
- TSAT

- S-iron

7.12.4 Pharmacokinetic Assessments

Blood for pharmacokinetic assessments will be obtained at baseline from 35 consecutive subjects in relation to treatment with iron isomaltoside and intensive ECG monitoring at selected sites. The time points for such sampling will be: pre-dose (at approximately -15 minutes), and post-dose at: 0.5, 1, 1.5, 2, 3, 4, 6, and 24 hours post-dose. The assessments and analyses will be described in a specific procedure description (sub-protocol).

7.13 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 1500 subjects will be recruited, and they will be randomised 2:1 to 1 of the following treatment groups:

- Group A: iron isomaltoside
- Group B: iron sucrose

The blocked randomisation of subjects to treatment arms will be stratified in order to balance the following: type of underlying disease (gastroenterology, gynaecology, oncology, and 'other') and baseline cardiovascular risk (history of myocardial infarction, stroke, or congestive heart failure, yes/no).

The procedure for preparing the randomisation list will be approved by the Global Trial Responsible Statistician before the randomisation 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
2. Subjects 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.
3. Subjects with:
 - a. Up to 1 month run-in phase indicating intolerance or lack of response to oral iron or
 - b. A documented history of intolerance to oral iron therapy to at least one month of ordinated oral iron therapy within 9 months** prior to trial enrolment or
 - c. Screening Hb measurement in Investigators' opinion was sufficiently low as to require rapid repletion of iron stores to minimize the risk of eventual blood transfusion***

4. Hb \leq 11 g/dL
5. TSAT $<$ 20 %
6. S-ferritin $<$ 100 ng/mL
7. Willingness to participate and signing the informed consent form (ICF)

*The aetiology for IDA should be documented in the medical history and verified in the source document.

**The intolerance to oral iron treatment within the last 9 months should be documented in the medical history and verified in the source document with signs and symptoms that lead to discontinuation of the oral iron therapy and precluded further use of oral iron therapy.

*** The Hb measurement that in Investigators' opinion was sufficiently low as to require rapid repletion of iron stores to minimize the risk of receiving a blood transfusion should be documented in the source document.

Additional inclusion criteria after the run-in period:

After the run-in period, subjects who fulfil the following additional eligibility criteria will be included:

4. Hb level \leq 11 g/dL
5. S-ferritin \leq 800 ng/mL
6. Lack of efficacy: Hb increase $<$ 1 g/dL at visit R4 (i.e. inadequate response to oral iron) and compliance to oral iron (pill counts), which needs to be \geq 67 %

Or

4. Hb level \leq 11 g/dL
5. S-ferritin \leq 800 ng/mL
6. Inability to tolerate oral iron, as per discretion of the Investigator

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. Anaemia predominantly caused by factors other than IDA according to Investigator's judgment
2. Hemochromatosis or other iron storage disorders
3. Known hypersensitivity reaction to any component of iron isomaltoside or iron sucrose
4. Previous serious hypersensitivity reactions to any IV iron compounds
5. Previously randomised in a clinical trial with iron isomaltoside
6. Received an investigational drug within 30 days of screening
7. During 10-day period prior to screening; has been treated with IV iron
8. Erythropoiesis stimulating agent (ESA) treatment within 30 days before the screening visit

9. During 30-day period prior to screening or during the trial period; has or will be treated with a red blood cell transfusion, radiotherapy, and/or chemotherapy
10. During 30-day period prior to screening or during the trial period; has or will require a surgical procedure that necessitated general anaesthesia
11. ALAT and/or ASAT > 3 times upper limit of normal (e.g. decompensated liver cirrhosis or active hepatitis)
12. Any non-viral infection
13. Required dialysis for treatment of CKD
14. Alcohol or drug abuse within the past 6 months
15. Estimated life expectancy of < 6 months or, for cancer patients, an Eastern Cooperative Oncology Group (ECOG) performance status >1
16. 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
17. 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 3 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 Investigator 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 isomalto-side

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.

Following IV administration, iron isomaltoside is rapidly taken up by the cells in the reticulo-endothelial 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.

Iron sucrose

Iron sucrose (Venofer[®]) is an aqueous complex of polynuclear iron (III)-hydroxide in sucrose for IV use. Iron sucrose injection has a molecular weight of approximately 34,000-60,000 Daltons [Venofer[®] prescribing information (USA), 01/2014 or local Summary of Product Characteristics (SmPC)].

Iron sucrose is provided as a brown, sterile solution in 5 mL single dose vials (100 mg elemental iron per 5 mL) and 10 mL single dose vials (200 mg elemental iron per 10 mL). Iron sucrose must be administered intravenously by push injections over approximately 2-5 minutes in this trial, which is an approved treatment course.

10.2 Dosage, Administration and Blinding of Trial Drug

The subjects will be randomised 2:1 to 1 of the following treatment groups:

- 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).
- Group B, iron sucrose will be administered as 200 mg undiluted IV push injections over approximately 2-5 minutes and repeated according to standard practice or physician choice up to a maximum of five times (1000 mg) within the first two weeks starting at baseline. A cumulative dose of 1000 mg is recommended. The cumulative dose of iron sucrose should be specified and documented at baseline.

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 iron sucrose 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 2015, more than 1700 patients 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.

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.

10.4 Side Effects of Iron Isomaltoside

Side effect for iron isomaltoside is described in Investigator's Brochure (current version).

10.5 Side Effects of Iron Sucrose

Side effects for iron sucrose are described in Venofer[®] prescribing information (USA), 01/2014 or local SmPC.

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 iron sucrose 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, except oral iron during the run-in period (nutritional supplementation including iron is allowed unless it is assumed as treatment of the subject's anaemia)
- ESA
- Blood transfusion

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 pa-

rameters (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 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 electronic case report form (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], for iron sucrose [Venofer[®] prescribing information (USA), 01/2014 or local SmPC], or for oral iron [prescribing information (USA), version applicable at the time of approval of the protocol] 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.

Screen failures: 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.

Randomised 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. 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.

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

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- 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 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.

Collection of AEs during the run-in period

During the run-in period only the following common AEs for iron sulphate will be collected and recorded as described above: Constipation, vomiting, abdominal pain, and diarrhoea.

All SAEs must be collected and recorded as described below.

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
Roervangsvej 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. Thus, the subjects may attend visit 3, 4, 5, and 6.

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 co-primary endpoints are treatment-emergent serious and/or severe non-serious hypersensitivity AEs and change in Hb from baseline to week 8.

The following hypotheses will be tested:

Safety:

The incidence of treatment-emergent serious and/or severe non-serious hypersensitivity AEs in the iron isomaltoside treatment group is less than 3 %.

$$H_{01}: \pi_{\text{iron isomaltoside}} \geq 3 \%$$

against the alternative:

$$H_{A1}: \pi_{\text{iron isomaltoside}} < 3 \%,$$

where, $\pi_{\text{iron isomaltoside}}$ denote the incidence of treatment-emergent serious and/or severe non-serious hypersensitivity AEs.

The null hypothesis will be tested against the alternative by constructing an unadjusted two-sided exact 95 % confidence interval (CI) of the incidence.

Efficacy:

$$H_{02}: \mu_{\text{iron isomaltoside}} - \mu_{\text{iron sucrose}} \leq -0.5 \text{ g/dL}$$

against the alternative:

$$H_{A2}: \mu_{\text{iron isomaltoside}} - \mu_{\text{iron sucrose}} > -0.5 \text{ g/dL},$$

where, $\mu_{\text{iron isomaltoside}}$ and $\mu_{\text{iron sucrose}}$ denote the change from baseline to week 8 in Hb.

The null hypothesis will be tested against the alternative by constructing a two-sided 95 % CI of the difference in change in Hb, deducted at week 8 from mixed model for repeated measures (MMRM).

15.2 Sample Size Determination

Safety:

Data from previous trials conducted with iron isomaltoside suggests that the incidence of treatment-emergent serious and/or severe non-serious hypersensitivity AEs for an IDA population can be expected to be approximately 1 % (IBD-01/IBD-02/CIA-01/PP-01: $n=3/341=0.9\%$, 95% CI: 0.2 %; 2.5 %). And similar for iron sucrose (CKD-03: $n=1/114=0.9\%$, 95% CI: 0.0 %; 4.8 %). A common incidence of 1.5 % will be assumed for the current trial.

As these are relatively rare events, an incidence of 0 % for placebo is assumed. Iron isomaltoside should be at most 50 % worse than the difference between iron sucrose and placebo, corresponding to a maximum relative risk of 2 ($1.5\% / (1.5\% - 0\%)^2$).

This trial will primarily assess the risk of the test drug under investigation. Arguing back from a relative risk of 2, gives that the upper bound of the 95 % CI for the incidence of treatment-emergent serious and/or severe non-serious hypersensitivity AEs should be at most 3 % ($2 \times 1.5\%$) for the iron isomaltoside treatment group.

Efficacy:

IDA-301 was a double-blind, placebo-controlled trial designed to compare the safety and efficacy of 1000 mg IV ferumoxytol to placebo. In this trial, 608 subjects were treated with ferumoxytol and 200 received placebo. The change in Hb from baseline to week 5 was the primary efficacy endpoint for the European Union regulators, and one of the secondary endpoints for U.S. regulators. The mean change was 2.6 g/dL (standard deviation (SD): 1.5) for IV ferumoxytol and 0.1 g/dL (SD: 0.9) for placebo. The estimated treated effect of IV ferumoxytol (i.e. the difference between ferumoxytol and placebo) was estimated to be approximately 2.5 g/dL with a 95 % CI ranging from 2.3 to 2.7 g/dL. The point estimate will be used as estimate of the treatment effect. Preserving 80 % of this effect is believed to provide reasonable assurance that iron isomaltoside is efficacious. Hence, the non-inferiority margin is set to $(1-0.8) \times 2.5 \text{ g/dL} \sim 0.5 \text{ g/dL}$.

Power:

The significance level is set to 5 %. With $n = 1000$ in the iron isomaltoside treatment group, there is 88 % power for demonstrating that the upper bound of the 95 % CI of the incidence of treatment-emergent serious and/or severe non-serious hypersensitivity AEs is less than 3 %. And with $n = 500$ in the iron sucrose treatment group, assuming no difference between the treatment groups, and assuming a common SD = 1.5 g/dL, there is 100 % power for demonstrating non-inferiority of the change in Hb from baseline to week 8, using a non-inferiority margin of -0.5 g/dL.

This yields a total power for demonstrating both co-primary endpoints of 88 %.

The CKD-04 trial will run in parallel with this trial and the sample size is the same, yielding a total of 2000 subjects to be treated with iron isomaltoside and 1000 with iron sucrose. In addition to the efficacy and safety analyses performed for this trial alone, an efficacy and safety assessment will be performed for the two trials combined. This is briefly described in Section 0.

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 randomised subjects. Subjects will be included as randomised. This will be the primary analysis set for evaluating efficacy.

Safety analysis set: The safety analysis set will include all randomised subjects who received at least one dose of the trial drug. This will be the analysis set for evaluating safety.

Full analysis set (FAS): The FAS will consist of all randomised subjects, received at least one dose of the trial drug, and have at least one post baseline Hb assessment. Subjects will be included as randomised.

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

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) current version. An AE will be regarded as treatment emergent AEs (TEAEs) if it occurs after administration of randomised treatment. Related or possible related AE's are defined as ADRs.

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:

- Non-treatment emergent AEs (defined as AEs collected before dosing including AEs reported for subjects never exposed to trial drug) in randomised subjects
- Treatment emergent AEs (non-serious and serious) in randomised subjects
- Treatment emergent SAEs in randomised subjects
- SAEs in non-randomised subjects
- ADRs

- AEs leading to dose reduction or withdrawal from treatment
- Fatal SAEs
- Serious or severe hypersensitivity reactions
- Composite cardiovascular AEs

15.5.1.1 Primary Analysis

The co-primary safety endpoint is treatment-emergent serious and/or severe non-serious hypersensitivity AEs. The SMQs/preferred terms are listed in Appendix A.

An exact two-sided 95 % CI of the incidence of treatment-emergent serious and/or severe non-serious hypersensitivity AEs in the iron isomaltoside treatment group will be constructed. If the upper bound of the 95 % CI is <3 %, the safety objective has been met.

In addition, as supportive information, the risk difference between iron isomaltoside and iron sucrose will be assessed by constructing a 95 % CI of the risk difference. Both an unadjusted CI (with continuity correction), and a CI adjusted for strata using the Cochran-Mantel-Haenszel method will be produced.

15.5.1.2 Secondary Analyses

The incidence of composite cardiovascular safety AEs will be tabulated and compared between the treatment groups by a Fisher's exact test.

The time to first composite cardiovascular safety AEs will be presented by a Kaplan-Meier plot, and the treatment groups will be compared by a log-rank test.

The incidence of treatment-emergent AEs, SAEs, ADR, and SARs will be tabulated and compared between the treatment groups by a Fisher's Exact Test.

15.5.1.3 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.

15.5.2 Efficacy Analyses

The co-primary efficacy endpoint will be analysed using a restricted maximum likelihood (REML)-based MMRM approach. All subjects in the ITT with post baseline Hb data will be included with their observed data. For subjects without post baseline Hb 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 iron sucrose), week, treatment-by-week interaction, strata, as well as the continuous, fixed covariates of baseline Hb value and baseline Hb-by-week interaction. An unstructured (co)variance structure will be used to model the within-subject errors. If, unexpectedly, this analysis fails to converge, the following structures will be applied, in the following order; first-order ante-dependence, heterogeneous compound symmetry, compound symmetry. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The primary comparisons will be the contrasts between iron isomaltoside and iron sucrose at week 8 based on the least squares means for the treatment-by-week interaction effect. The estimated mean difference based on this model will be reported with two-sided symmetric 95 % CI, and if the lower bound of the 95 % CI is > -0.5

g/dL, the efficacy objective has been met. If the lower bound of the two-sided 95 % CI is > 0 g/dL superiority will be declared, and the p -value for the test of superiority will be presented.

As sensitivity, the analysis above will be repeated for the FAS and PP analysis sets.

Some level of data missingness is expected, and the primary analysis (MMRM) is valid under the assumption that the data is Missing at Random (MAR). Simulation trials do suggest that MMRM is robust to accommodate some level of data Missing Not at Random. Since it is unclear how the level of missingness of this type of data will influence the outcome at this stage, choosing a pre-specified primary analysis valid under MNAR accurately will be very difficult. As such, sensitivity analyses valid under relevant cases of data MNAR will be performed. In particular, pattern-mixture models will be used. Different delta (imputation of how much worse response subjects who discontinue would have compared to those who complete the trial and who have the same profile up to time to withdrawal) will be applied as described by C. H. Mallinckrodt, Q. Lin, and G. Molenberghs [Mallinckrodt *et al.*, 2012]. These analyses will be performed for the ITT, FAS, and PP analysis sets.

The proportion of subjects with an Hb increase of ≥ 2 g/dL from baseline to any time from week 1 to week 8 will be compared between treatment groups using a logistic regression model with treatment and strata as fixed effects. Subjects without post baseline Hb values will be set as failures. The estimated treatment ratio of iron isomaltoside versus iron sucrose will be presented with 95 % CIs and corresponding p -value.

Time to change in Hb increase ≥ 2 g/dL will be presented by a Kaplan-Meier plot, and the treatment groups will be compared by a log-rank test. Subjects without post baseline Hb values will be set as censored at day 0.

The proportion of subjects who achieve Hb level of > 12 g/dL at any time from week 1 to week 8, the proportion of subjects who achieve an increase in Hb concentration ≥ 2 g/dL at any time from week 1 to week 8, and the proportion of subjects who achieve s -ferritin level of ≥ 100 ng/mL and TSAT of 20-50 % at any time from week 1 to week 8 will be analysed by a logistic regression model similar to above. Subjects without Hb values at week 1-8 will be set as failures.

The change in concentrations of Hb to weeks 1, 2, and 4, and change in s -ferritin, TSAT, and s -iron from baseline to weeks 1, 2, and 8, and change in fatigue symptoms (FACIT) will be estimated by MMRM models similar to the one described for the co-primary efficacy endpoint.

Pharmacoeconomics will be assessed by the ISDR questionnaire and health care resource use questionnaire and summarised descriptively.

15.6 Combined Analysis of IDA-03 and CKD-04

The two trials IDA-03 and CKD-04 will run in parallel. With $n=1000$ treated with iron isomaltoside and $n=500$ treated with iron sucrose, each trial is powered to show that the incidence of serious and/or severe hypersensitivity AEs in the iron isomaltoside group is less than 3 % and, with a non-inferiority margin of -0.5 g/dL, to demonstrate non-inferiority of iron isomaltoside versus iron sucrose for change in Hb to week 8.

Pooled analyses will be performed of the two trials.

For safety, in addition to estimating the absolute risk (incidence and 95 % CI) of iron isomaltoside, a non-inferiority analysis will be performed of iron isomaltoside versus iron su-

crose. For iron sucrose, a similar rate of 1.5 % will be assumed. As iron isomaltoside should be no worse than 3 %, the non-inferiority margin will be set to 1.5 % points. The non-inferiority assessment will be performed by estimation of the risk difference and the associated 95 % CI, adjusting for trial using the Cochran-Mantel-Haenszel method. With a total of 2000 subjects treated with iron isomaltoside, and 1000 subjects treated with iron sucrose, assuming common incidences of 1.5 %, and using a significance level of 5 %, the power to demonstrate non-inferiority is 87 %.

As sensitivity, the incidence will be estimated from a Kaplan-Meier curve of time to serious and/or severe hypersensitivity AEs. The log-log transformation will be used to estimate the standard errors for each treatment group, and the 95 % CI will be constructed by pooling these standard errors.

For efficacy, the same non-inferiority assessment as in the individual trials will be performed, including the specified sensitivity analyses. A similar MMRM model as for the individual trials will be applied, with trial added as fixed factor. The power for demonstrating efficacy is 100 %.

Hence, with a total of 2000 subjects treated with iron isomaltoside, and 1000 subjects treated with iron sucrose, the combined power of demonstrating the two primary endpoints is 87 %.

Similar to the individual trials, if the upper bound of two-sided 95 % CI of the risk difference (iron isomaltoside - iron sucrose) < 0 for the incidence of serious and/or severe hypersensitivity, or the lower bound of two-sided 95 % CI of the mean difference (iron isomaltoside - iron sucrose) in change in Hb from baseline to week 8 is 0 g/dL superiority will be declared, and the *p*-values for the test of superiority will be presented.

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 the 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 a 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.

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 GCP deviations.

Out of visit windows will be registered as minor deviations if they are < 14 days.

The following will be assessed as major protocol deviation:

- Out of visit window of ≥ 14 days after the final visit (i.e. ≥ 70 days after baseline)
- Intake of prohibited medication
- Treatment compliance outside the 80-120 % range (the calculation of compliance for iron sucrose is based upon the cumulative dose recorded at baseline)
- 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
- Global trial management
- Global medical monitoring
- QC/Regulatory
- 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 on a monthly basis.

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
- Head of Drug Safety
- QC/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
- Pharmacosmos CEO

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 15 years.

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.

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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.

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 co-primary endpoints and key secondary endpoints will be uploaded on public websites in according to national requirements. Key secondary endpoints in the trial are the following:

- Change in concentrations of Hb from baseline to weeks 1, 2, and 4
- Change in concentrations of *s*-ferritin and TSAT from baseline to weeks 1, 2, 4, and 8

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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
- Periobital oedema
- Pruritus
- Pruritus allergic

- 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

Adjudicated composite cardiovascular endpoints

1. Death due to any cause will be adjudicated as the date the subject is pronounced dead.

2. Myocardial infarction: A myocardial infarction (MI) will be defined as the presence of the characteristic changes in cardiac enzyme markers in the setting of either temporally related symptoms of an acute coronary syndrome or electrocardiographic (ECG) changes consistent with either ischemia or infarction.

Cardiac enzyme markers indicative of an MI will include:

- An appropriate rise and fall in serum troponin (I or T) or creatine kinase-MB where at least 1 value is $\geq 2 \times$ upper limit of normal (ULN). Where only 1 value has been measured, if it is $\geq 2 \times$ ULN, an event may be adjudicated based on the totality of the clinical evidence.
- Where only total creatine phosphokinase is measured, serial changes (i.e. at least 2 values) need to be $\geq 2 \times$ ULN.

Symptoms indicative of ischemia will need to have been present for ≥ 10 minutes and may include chest pain, chest pressure, or chest tightness. Dyspnoea, diaphoresis, or nausea may be considered symptoms of ischemia and will be judged based on the totality of the clinical evidence.

ECG changes will be defined as:

- New Q waves in 2 or more contiguous leads
- Evolving ST-segment to T-wave changes in 2 or more contiguous leads + (such as ≥ 0.5 mm transient ST-segment depression)
- New left bundle branch block
- 1 mm ST-segment elevation in 2 or more contiguous leads

3. Stroke: A stroke is defined as a focal neurological deficit of sudden onset that is not reversible within 24 hours that results from a vascular cause involving the central nervous system and is not due to another readily identifiable cause (i.e. brain tumour or trauma). Strokes will be sub-classified as haemorrhagic, ischaemic, or unknown.

4. Unstable angina requiring hospitalization: Unstable angina requiring hospitalization will be defined as ischemic symptoms meeting the following criteria:

1. Lasting ≥ 10 minutes and considered to be myocardial ischemia on final diagnosis
AND
2. Requiring an unscheduled visit to a health care facility and overnight admission (does not include chest pain observation units)
AND
3. At least one of the following:
 - New dynamic ECG changes

- Ischemia evidence on stress testing with or without cardiac imaging
- Angiographic evidence of $\geq 70\%$ lesion and/or thrombus in an epicardial coronary artery

5. Congestive heart failure requiring hospitalization or medical intervention will meet the following criteria:

1. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12-hour stay (or a date change if the time of admission/discharge is not available)

AND

2. Clinical manifestation of congestive heart failure including at least one of the following: new or worsening dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, oedema, pulmonary basilar crackles, jugular venous distension, or radiological evidence of worsening heart failure

AND

3. Additional/increased therapy
 - a. Intravenous treatment with diuretic, inotrope, or vasodilator therapyOR
 - b. Mechanical or surgical intervention (mechanical circulatory support, heart transplantation, or ventricular pacing to improve cardiac function) or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure

6. Arrhythmia will be defined as any symptomatic deviation from normal sinus rhythm experienced by the subject that results in an evaluation by a health care provider. The evaluation may include a physical exam during an outpatient visit, an ECG, or a hospital admission. Arrhythmias may include any conduction abnormality, atrioventricular heart block, prolongation of QTc interval, supraventricular/nodal arrhythmia, vasovagal episode, ventricular arrhythmia, or other cardiovascular arrhythmia.

7. Hypertension

- During the observation period immediately following trial drug administration, hypertension will be defined as an increase in systolic blood pressure > 20 mm Hg that results in a value > 180 mm Hg or an increase in diastolic blood pressure > 15 mm Hg that results in a value > 105 mm Hg
- Following the release of a subject from the trial visit during which they are receiving medication, hypertension will be defined as requiring an unscheduled outpatient health care visit, a hospital admission, or a change in medical therapy (e.g. administration of antihypertensives) in conjunction with the objective criteria, a rise in blood pressure (an increase in systolic blood pressure > 20 mm Hg that results in a value > 180 mm Hg or an increase in diastolic blood pressure > 15 mm Hg that results in a value > 105 mm Hg)

8. Hypotension

- During the observation period immediately following trial drug administration, hypotension will be defined as a decrease in systolic blood pressure > 20 mm Hg that results in a value < 90 mm Hg or a decrease in diastolic blood pressure > 15 mm Hg that results in a value < 50 mm Hg.
- Following the release of a subject from the trial visit during which they are receiving medication, hypotension will be defined as requiring an unscheduled outpatient health care visit, a hospital admission, or a change in medical therapy (e.g. fluid/volume repletion, holding of antihypertensives) in conjunction with the objective criteria, a decrement in blood pressure (a decrease in systolic blood pressure > 20 mm Hg that results in a value < 90 mm Hg or a decrease in diastolic blood pressure > 15 mm Hg that results in a value < 50 mm Hg).