CLINICAL TRIAL PROTOCOL

An open-label, multicentre, extension trial to assess the safety of re-dosing of intravenous iron isomaltoside (Monofer®)

Trial ID: P-Monofer-IDA/CKD-EXT-01

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

Protocol Version: Version 1, 7 June 2016

Protocol Version: Version 2 (amendment 1), 14 June 2017

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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

An open-label, multicentre, extension trial to assess the safety of re-dosing of intravenous iron isomaltoside (Monofer®)

Trial design

The trial is a prospective, open-label, multi-centre, extension trial of the lead-in trials P-Monofer-IDA-01, P-Monofer-IDA-03, and P-Monofer-CKD-04 to assess the safety profile of iron isomaltoside 1000 (Monofer®, Pharmacosmos, Holbæk, Denmark) in subjects at 3 and 6 months after re-dosing.

Subjects will be re-dosed with 1000 mg iron isomaltoside.

Phase of trial

The trial is a phase III trial.

Background

Iron deficiency anaemia (IDA) is often associated with many chronic diseases such as renal diseases, cancer, infections, chronic heart failure, and inflammatory bowel disease.

Subjects are often treated with erythropoiesis stimulating agents (ESAs) in order to stimulate erythropoiesis. This therapy requires rapid mobilisation of iron reserves in order to meet the demands of new red blood cell (RBC) growth. Despite normal or even increased iron stores, the demands of this therapy can outstrip the body's ability to mobilise iron stores resulting in "functional iron deficiency".

IDA can have a substantial medical and quality of life (QoL) burden on the subjects, and treatment of these subjects includes treatment of its underlying cause and restoration of normal haemoglobin (Hb) concentrations and iron stores. Iron replacement can be accomplished by the oral or parenteral routes. Intravenous (IV) iron offers a rapid and efficient means of iron correction, and it is superior to oral iron therapy in many circumstances. Treatment with oral iron may be adequate for some patients, but intolerance, abnormal absorption due to inflammation, noncompliance, and large iron deficits may lead to an inadequate treatment of the anemia with oral iron. International guidelines recommend IV iron preparations as the preferred option in the correction of IDA in several of these circumstances and when there is a high iron demand, since it is more effective, better tolerated, and improves QoL to a greater extent than oral iron supplements.

Most trials with IV iron have been 4-12 weeks trials and long-term trials are warranted to follow-up on long-term safety. This trial is a 6-months extension trial of P-Monofer-IDA-01, P-Monofer-IDA-03, and P-Monofer-CKD-04 trials where the aim is to evaluate the safety and efficacy of IV iron isomaltoside re-dosing.

Objectives

The primary objective of the trial is to evaluate the safety of IV iron isomaltoside after re-dosing.

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

- Increase in Hb

- Other relevant iron related biochemical parameters

Endpoints

The primary endpoint is the number of adverse drug reaction (ADR).

The secondary safety endpoints are the following:

- Serious or severe hypersensitivity reaction starting on or after the treatment with iron isomaltoside (i.e. treatment-emergent). The hypersensitivity terms are defined as standardised Medical Dictionary for Regulatory Activities query (SMQ) terms (including four additional terms) in Appendix A.
- Composite cardiovascular adverse events (AEs) starting on or after the treatment with iron isomaltoside (i.e. treatment-emergent). The adjudicated composite AEs includes the following:
  - Death due to any cause
  - Non-fatal myocardial infarction
  - Non-fatal stroke
  - Unstable angina requiring hospitalization
  - Congestive heart failure requiring hospitalization or medical intervention
  - Arrhythmias
  - Hypertension
  - Hypotension

  The AEs will be adjudicated by an independent clinical events classification committee (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 month 6

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

The efficacy endpoints are the following:

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

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 by an independent clinical events classification committee (described in a separate adjudication charter)
- Physical examinations, measurements of vital signs, height, weight, ECG, and safety

laboratory parameters

Efficacy assessments

The trial includes the following efficacy assessments:

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

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 6 months including 5 visits; screening visit, baseline visit, 2 weeks visit, 3 months visit, and 6 months visit.

Subject population

Subjects from selected sites in the lead-in trials will be offered to participate in this extension trial if they fulfil the following eligibility criteria:

Inclusion criteria:

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

1. Completed one of the lead-in trials
2. Randomised and dosed with iron isomaltoside in one of the lead-in trials. The dose given needs to be in compliance, i.e. within 80-120 % of the cumulative dose.
3. Having a Hb of ≤ 11 g/dL
4. Screening *s*-ferritin ≤ 100 ng/mL, or ≤ 300 ng/mL if TSAT ≤ 30 %
5. Life expectancy beyond 18 months by Investigator's judgement
6. Willingness to participate and signing the informed consent form

Exclusion criteria:

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

1. IV iron treatment between the lead-in trial and screening
2. 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
3. Received an investigational drug within 30 days of screening
4. Alanine aminotransferase (ALAT) and/or aspartate aminotransferase (ASAT) > 3 times upper limit of normal (e.g. decompensated liver cirrhosis or active hepatitis)
5. Undergoing dialysis for treatment of CKD or under consideration for dialysis during the trial period
6. 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
7. 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

Trial treatment

Subjects will be dosed with a single infusion of 1000 mg iron isomaltoside diluted in 100 mL 0.9 % sodium chloride and given over approximately 20 minutes. No test dose will be applied.

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.

Statistical analyses

No sample size calculations have been performed for this extension trial. It is anticipated that 100 subjects will be recruited with at least 25 subjects with IDA and at least 25 NDD-CKD subjects with IDA from the three lead-in trials, P-Monofer-IDA-01, P-Monofer-IDA-03, and P-Monofer-CKD-04, and followed for 6 months safety follow-up.

The incidence of treatment-emergent ADRs and SARs will be presented, including two-sided 95 % confidence interval (CI).

Safety and efficacy assessments will be summarised descriptively.

Summaries will be prepared with respect to two baselines: Baseline in lead-in trial, and baseline in this extension trial. Summaries will be prepared overall and by lead-in trial.

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

1 ABBREVIATIONS AND DEFINITIONS OF TERMS

1.1 Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALAT	Alanine Aminotransferase
ASAT	Aspartate Aminotransferase
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CKD	Chronic Kidney Disease
CRA	Clinical Research Associate
CRP	C-Reactive Protein
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ESA	Erythropoiesis Stimulating Agents
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
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCT	Trial Core Team
TEAE	Treatment Emergent Adverse Event
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 a common problem associated with many chronic diseases such as chronic kidney disease (CKD), cancer, infections, chronic heart failure (CHF), and inflammatory bowel disease (IBD). It is also common in pregnant women and occurs in the elderly. IDA is primarily caused by chronic blood loss, poor diet, or impaired gastrointestinal iron absorption. The major causes of anaemia in CKD subjects are iron and erythropoietin deficiencies and a decreased responsiveness to the actions of erythropoietin [Mehdi & Toto, 2009].

Subjects are often treated with erythropoiesis stimulating agents (ESAs) in order to stimulate erythropoiesis. This therapy requires rapid mobilisation of iron reserves in order to meet the demands of new red blood cell (RBC) growth. Despite normal or even increased iron stores, the demands of this therapy can outstrip the body's ability to mobilise iron stores resulting in "functional iron deficiency" [Hotta *et al.*, 1991].

IDA can have a substantial medical and quality of life (QoL) burden on the subjects, and treatment of these subjects includes treatment of its underlying cause and restoration of normal haemoglobin (Hb) concentrations and iron stores. Iron replacement can be accomplished by the oral or parenteral routes. Intravenous (IV) iron offers a rapid and efficient means of iron correction, and it is superior to oral iron therapy in many circumstances [Dignass *et al*., 2015]. Treatment with oral iron may be adequate for some patients, but intolerance, abnormal absorption due to inflammation, noncompliance, and large iron deficits may lead to an inadequate treatment of the anemia with oral iron [Henry, 2006]. International guidelines recommend IV iron preparations as the preferred option in the correction of IDA in several of these circumstances and when there is a high iron demand, since it is more effective, better tolerated, and improves QoL to a greater extent than oral iron supplements [Charytan *et al*., 2005; Gasche *et al*., 2007; KDIGO guideline, 2012; Dignass *et al*., 2015].

Most trials with IV iron have been 4-12 weeks trials and long-term trials are warranted to follow-up on long-term safety after re-dosing. One randomised, comparative, open-label, 5-weeks trial with iron isomaltoside 1000 (Monofer®, Pharmacosmos, Holbæk, Denmark) has been carried out (P-Monofer-IDA-01) and two randomised, comparative, open-label, 8-weeks trials are going to be initiated in subjects with IDA (P-Monofer-IDA-03) and NDD-CKD subjects with IDA (P-Monofer-CKD-04). This trial is a 6-months extension trial of P-Monofer-IDA-01, P-Monofer-IDA-03, and P-Monofer-CKD-04 trials where the aim is to evaluate the safety and efficacy of IV iron isomaltoside re-dosing.

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 ^{13}C 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.

Most trials with IV iron have been 4-12 weeks trials and long-term trials are warranted to follow-up on long-term safety. One randomised, comparative, open-label, 5-weeks trial with iron isomaltoside 1000 has been carried out (P-Monofer-IDA-01) and two randomised, comparative, open-label, 8-weeks trials with iron isomaltoside is going to be initiated in subjects with IDA (P-Monofer-IDA-03) and NDD-CKD subjects with IDA (P-Monofer-CKD-04). This trial is a 6-months extension trial of P-Monofer-IDA-01, P-Monofer-IDA-03, and P-Monofer-CKD-04 trials where the aim is to evaluate the safety and efficacy of IV iron isomaltoside re-dosing. Some subjects from the lead-in trials (P-Monofer-IDA-01, P-Monofer-IDA-03, and P-Monofer-CKD-04) will need re-dosing in order to maintain their Hb above a certain threshold. Hence, the intention in this trial is to re-dose subjects when Hb is going down, but not necessarily to a more severe stage of anaemia. On the other hand it is the intention not to expose subjects if there is an indication that there iron related parameters are too high.

3 TRIAL DESIGN

The trial is a prospective, open-label, multi-centre, extension trial of the lead-in trials P-Monofer-IDA-01, P-Monofer-IDA-03, and P-Monofer-CKD-04 to assess the safety profile of iron isomaltoside in subjects at 3 and 6 months after re-dosing. For the individual subject, duration of the trial will be approximately 6 months including 5 visits; screening visit, baseline visit, 2 weeks visit, 3 months visit, and 6 months visit.

Subjects will be re-dosed with 1000 mg iron isomaltoside.

4 TRIAL OBJECTIVES

4.1 Primary Safety Objectives

The primary objective of the trial is to evaluate the safety of IV iron isomaltoside after re-dosing.

4.2 Secondary Efficacy Objectives

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

- Increase in Hb
- Other relevant iron related biochemical parameters

5 TRIAL ENDPOINTS

5.1 Primary Safety Endpoint

The primary endpoint is the number of adverse drug reaction (ADR).

5.2 Secondary Safety Endpoints

The secondary safety endpoints are the following:

- Serious or severe hypersensitivity reaction starting on or after the treatment with iron isomaltoside (i.e. treatment-emergent). The hypersensitivity terms are defined as standardised Medical Dictionary for Regulatory Activities query (SMQ) terms (including four additional terms) in Appendix A.
- Composite cardiovascular adverse events (AEs) starting on or after the treatment with iron isomaltoside (i.e. treatment-emergent). The adjudicated composite AEs includes the following:
  - Death due to any cause
  - Non-fatal myocardial infarction
  - Non-fatal stroke
  - Unstable angina requiring hospitalization
  - Congestive heart failure requiring hospitalization or medical intervention
  - Arrhythmias
  - Hypertension
  - Hypotension

  The AEs will be adjudicated by an independent clinical events classification committee (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 month 6

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

5.3 Efficacy Endpoints

The efficacy endpoints are the following:

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

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 5 visits.

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

Table 1: Trial flowchart

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

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

b. All trial assessments should be done before administration of the trial drug unless otherwise stated in Section 7.
c. The final visit form may be filled in at any time of the trial if the subject is withdrawn.
d. Laboratory tests taken at visit 6 of the lead-in trials P-Monofer-IDA-03 and P-Monofer-CKD-04 will be considered as screening values for the extension trial if they are collected ≤14 days before the screening visit.

6.3 Visit 1 (Screening)

Visit 1 (screening) will be conducted within 14 days prior to visit 2 (baseline). The following will be done:

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

6.4 Visit 2 (Baseline)

Visit 2 (baseline) will be conducted a maximum of 14 days after the screening visit. The following will be assessed:

- Inclusion and exclusion criteria checked
- Pregnancy test, if applicable
- Recording of relevant medical history, including specific assessment of 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
- ECG
- Safety laboratory tests
- Efficacy laboratory tests
- Treatment with iron isomaltoside
- AE evaluation and recording

6.5 Visit 3

Visit 3 will be conducted 2 weeks (± 2 days) after baseline. 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

6.6 Visit 4

Visit 4 will be conducted 13 weeks (± 3 days) after baseline. 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

6.7 Visit 5

Visit 5 will be conducted 26 weeks (± 4 days) after baseline. 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
- Safety laboratory tests
- Efficacy laboratory tests
- AE evaluation and recording
- Completing the final visit form

7 TRIAL ASSESSMENTS

7.1 Demographic and Baseline Assessments

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

7.2 Pregnancy Test

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

7.3 Relevant Medical History

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

7.4 Concomitant Medication

If the subject is receiving any concomitant medication it will be recorded at the baseline visit. Changes in concomitant medication will be recorded in the subsequent visits during the trial. The following will be collected: 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 during infusion of iron isomaltoside: approximately 0-10 minutes before infusion, during infusion, 5-15 minutes, and 20-40 minutes after the infusion has ended.

7.9 Electrocardiogram

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

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

7.10 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.

7.10.1 Eligibility Laboratory Assessments

The following eligibility laboratory assessments will be performed:

- Complete haematology set: Hb, leucocytes/white blood cells (WBC), erythrocytes/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
    - Aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT)

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

7.10.2 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
    - C-reactive protein (CRP)

7.10.3 Efficacy Laboratory Assessments

The following efficacy laboratory parameters will be analysed:

- Hb
- *S*-ferritin
- TSAT
- *S*-iron

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

8.2 Inclusion Criteria

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

1. Completed one of the lead-in trials
2. Randomised and dosed with iron isomaltoside in one of the lead-in trials. The dose given needs to be in compliance, i.e. within 80-120 % of the cumulative dose.
3. Having a Hb of ≤ 11 g/dL
4. Screening *s*-ferritin ≤ 100 ng/mL, or ≤ 300 ng/mL if TSAT ≤ 30 %
5. Life expectancy beyond 18 months by Investigator's judgement
6. Willingness to participate and signing the informed consent form (ICF)

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. IV iron treatment between the lead-in trial and screening
2. 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
3. Received an investigational drug within 30 days of screening
4. ALAT and/or ASAT > 3 times upper limit of normal (e.g. decompensated liver cirrhosis or active hepatitis)
5. Undergoing dialysis for treatment of CKD or under consideration for dialysis during the trial period
6. 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
7. 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

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

If a subject does not fulfil the inclusion/exclusion criteria (screen failure), they may be re-screened up to three times. 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 isomaltoside

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

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

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

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

10.2 Dosage, Administration and Blinding of Trial Drug

Subjects will be dosed with a single infusion of 1000 mg iron isomaltoside diluted in 100 mL 0.9 % sodium chloride and given over approximately 20 minutes. No test dose will be applied.

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 are further described in the Drug Handling Plan.

10.3 Dose Rationale

In the present trial, subjects will be given 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 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 are further described in the Drug Handling Plan.

10.6 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.

10.7 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.

ESA may be administered to the subjects if they were receiving ESA treatment in the lead-in trial. ESA treatment must be kept stabile (+/- 20%) both in the lead-in trial and during the extension trial. If the ESA treatment is terminated between the lead-in trial and this extension trial, the wash-out period is 4 weeks before the screening visit in this trial.

11.2 Prohibited Medications and Non-drug Therapies

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

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

- Any iron supplementation other than investigational drug (nutritional supplementation including iron is allowed unless it is assumed as treatment of the subject's anaemia)
- Blood transfusion

ESAs are also prohibited medication unless the subject was treated with ESA in the lead-in trial or has received a stable dose (+/- 20 %) 4 weeks before the screening visit in this trial.

12 ADVERSE EVENTS

12.1 Definition of Adverse Events

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

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

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

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

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, and 5.

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 infor-

mation. 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

No formal hypotheses will be tested in this 6 months safety extension trial.

15.2 Sample Size Determination

No sample size calculations have been performed for this extension trial. It is anticipated that 100 subjects will be recruited with at least 25 subjects with IDA and at least 25 NDD-CKD subjects with IDA from the three lead-in trials, P-Monofer-IDA-01, P-Monofer-IDA-03, and P-Monofer-CKD-04, and followed for 6 months safety follow-up

15.3 Data Analysis Sets

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

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

Intention to treat (ITT) analysis set: The ITT analysis set will include all subjects. This will be the primary analysis set for evaluating efficacy.

Full Analysis Set (FAS): The FAS will consist of all subjects who received at least one dose of the trial drug in the lead-in trial, and have at least one post baseline Hb assessment.

Per protocol (PP) analysis set: The PP analysis set will include all the subjects in the FAS who do not have any major protocol deviation of clinical or statistical significance. Major protocol deviations are defined in Section 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 Statistical Analyses

Summary tables and descriptive statistics will be applied to demographics, efficacy, and safety data. Concomitant medications and medical history will be listed by subject.

Summaries will be prepared with respect to two baselines: Baseline in lead-in trial, and baseline in this extension trial. Summaries will be prepared overall and by lead-in trial.

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

15.6 Safety Analyses

The incidence of treatment-emergent ADRs and SARs will be presented, including two-sided 95 % confidence interval (CI).

AEs will be classified according to the time of onset:

- *Non-treatment emergent AE* – an AE that starts after the subject has signed the ICF but before the subject receives iron isomaltoside in this extension trial
- *Treatment emergent AE* (TEAE) – an AE that starts after the subject receives iron isomaltoside in this extension trial

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) current version. Related or possible related AE's are defined as ADRs.

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 in treated subjects
- TEAEs (non-serious and serious)
- Treatment emergent SAEs
- SAEs in subjects not receiving treatment in the extension trial (e.g. screen failures)
- ADRs
- AEs leading to dose reduction or withdrawal from treatment
- Fatal SAEs
- Serious or severe hypersensitivity reactions
- Composite cardiovascular AEs

Physical examinations and measurements of vital signs, height, weight, ECG, and safety laboratory parameters will be tabulated by visit.

Efficacy Analyses

Change in Hb, *s*-ferritin, TSAT, and *s*-iron from baseline (lead-in and extension) to week 2 and months 3 and 6 will be tabulated.

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 recon-

struction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). Source data location list needs to be filled in and maintained by the Investigator during the trial.

16.2 Data Management

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

The site staff will be trained before they have access to the eCRF and 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 < 30 days.

The following will be assessed as major protocol deviation:

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

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 regenerating 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.

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 primary endpoint 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 Hb from baseline to week 2 and months 3 and 6
- Change in *s*-ferritin and TSAT from baseline to week 2 and months 3 and 6

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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 ≥ 2 × upper limit of normal (ULN). Where only 1 value has been measured, if it is ≥ 2 × 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 ≥ 2 × 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 ≥ 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 therapy

    OR

    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).