# SYNOPSIS

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| **Name of company**<br>Pharmacosmos A/S | Individual Study Table Referring to Part of the Dossier:<br><br>Volume:<br><br>Page: | (For National Authority Use only) |
| **Name of finished product**<br>Monofer® | | |
| **Name of active ingredient**<br>Iron isomaltoside 1000 | | |

**Title of study**

A phase III, randomised, comparative, open-label study of intravenous iron isomaltoside 1000 (Monofer®) administered by infusions or repeated bolus injections in comparison with oral iron sulphate in inflammatory bowel disease subjects with iron deficiency anaemia

**Investigators**

The list of Investigators is presented in the Appendix 16.1.4.

**Study centres**

The study was conducted at 36 centres, [redacted].

**Publication (reference)**

Not applicable

**Studied period**

First Subject First Visit (FSFV): 2 December 2009

Last Subject Last Visit (LSLV): 30 July 2012

**Phase of development**

Phase III

**Study design**

The study was a phase III study. The study was conducted in subjects diagnosed with Inflammatory Bowel Disease (IBD) with Iron Deficiency Anaemia (IDA). The enrolment period of the study was more than 2 years (December 2009-May 2012). The study duration for the individual subject was approximately 8 weeks and each subject attended 7 visits. The subjects were randomised to 1 of 3 treatment groups:

- Group A: Iron isomaltoside 1000
  - Group A1: administered as Intravenous (IV) infusions
  - Group A2: administered as IV bolus injections
- Group B: Iron sulphate administered orally

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**Objectives**

Primary objective

- To demonstrate that IV iron isomaltoside 1000 is non-inferior to oral iron sulphate in reducing IDA secondary to IBD, evaluated as the ability to increase Haemoglobin (Hb)

Secondary objectives

- To assess other relevant haematology and biochemical parameters during the study
- Quality of Life (QoL) assessment by questionnaire
- Assessment of Restless Legs Syndrome (RLS) symptoms and change in these symptoms during the study

Safety objective

- To assess safety of IV iron isomaltoside 1000 compared to oral iron sulphate

**Endpoints**

Primary endpoint

- Change in Hb concentration from baseline to week 8

Secondary endpoints

- Number of subjects who achieved target limits of Hb (men 13-18 g/dL, women 12-16 g/dL) and had a change in Hb concentration > 1.0 g/dL, serum (*s*-) ferritin (100-800 µg/L) and had achieved Transferrin Saturation (TSAT) (20-50 %) at week 2, 4, or 8
- Change in Hb concentration from baseline to week 2 and 4
- Change in concentrations of *s*-iron, *s*-ferritin, and TSAT from baseline to week 1, 2, 4, and 8
- Number of subjects who discontinued study because of lack of response or intolerance of investigational drugs
- Change in total QoL score from baseline to week 4 and 8
- Change in RLS symptoms (RLS score) from baseline to week 8 in subjects with RLS symptoms at baseline
- Number of subjects who experienced any adverse drug reaction (ADR), including any suspected unexpected serious adverse reaction

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**Additional exploratory endpoints**

- Change in Hb concentration from baseline to week 1, 2, 3, 4, and 8 analysed by region (Europe versus Asia)
- Change in Hb concentration from baseline to week 1, 2, 3, 4, and 8 analysed by cumulative dose (< 1000 mg and ≥ 1000 mg)
- Change in Hb concentration from baseline to week 1, 2, 3, 4, and 8 analysed by region (Europe versus Asia) and cumulative dose (< 1000 mg and ≥ 1000 mg)
- Change in Hb concentration from baseline to week 1, 2, 3, 4, and 8 analysed by IBD (Crohn's disease versus ulcerative colitis)
- Number of subjects who had an increase in Hb concentration of > 2.0 g/dL
- Change in *s*-ferritin and TSAT concentration from baseline to week 1, 2, 3, 4, and 8 analysed by region (Europe versus Asia)
- Change in *s*-ferritin and TSAT concentration from baseline to week 1, 2, 3, 4, and 8 analysed by cumulative dose (< 1000 mg and ≥ 1000 mg)
- Change in *s*-ferritin and TSAT concentration from baseline to week 1, 2, 3, 4, and 8 analysed by region (Europe versus Asia) and cumulative dose (< 1000 mg and ≥ 1000 mg)
- Change in s-ferritin concentration from baseline to week 1, 2, 3, 4, and 8 analysed by IBD (Crohn's disease versus ulcerative colitis)

**Efficacy assessments**

- Hb concentration
- Concentrations of *s*-ferritin, *s*-iron, TSAT[#]
- QoL
- Change in RLS symptoms, if these were present in a subject

[#]Additionally total iron binding capacity (TIBC) was originally mentioned in the protocol as an efficacy assessment but does not correspond to an efficacy endpoint. Further haemosiderin was originally mentioned in the protocol but was decided not to be assessed during the study due to logistical considerations.

**Safety assessments**

- Adverse events (AEs) were collected and evaluated for relatedness to study drug, severity, seriousness, and expectedness. They were reported to authorities and followed-up according to international and local requirements

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- Vital signs, standard safety haematology and biochemical laboratory parameters (e.g. electrolytes, leucocytes, and transaminases)

**Study population**

560 subjects with a diagnosis of IBD along with IDA were screened and 338 of these were randomised in the study. The subjects had to fulfil the following eligibility criteria in order to be included in the study:

Inclusion criteria

1. Men and women aged more than 18 years
2. Subjects diagnosed with IBD and mild to moderate disease activity (defined as a score of less than or equal to 5 on the Harvey-Bradshaw index for Crohn's disease and a Mayo score (sub-score without endoscopy) of less than or equal to 6 for ulcerative colitis)
3. Hb < 12 g/dL (7.45 mmol/L)
4. TSAT < 20 %
5. Life expectancy beyond 12 months
6. Willingness to participate after signing informed consent

*S*-ferritin was chosen not to be an inclusion criterion as the cut-off level was highly dependent upon the disease.

Exclusion criteria

1. Anaemia predominantly caused by factors other than IDA
2. Iron overload or disturbances in utilisation of iron (e.g. haemochromatosis and haemosiderosis)
3. Drug hypersensitivity (i.e. previous hypersensitivity to iron dextran, iron mono- or disaccharide complexes, or to iron sulphate)
4. Known hypersensitivity to any excipient(s) in the investigational drug products
5. History of multiple allergies
6. Active intestinal tuberculosis
7. Active intestinal amoebic infections
8. Decompensated liver cirrhosis and hepatitis (alanine aminotransferase > 3 times upper limit of normal)

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9. Acute infections (assessed by clinical judgement) supported with white blood cells and C-reactive protein
10. Rheumatoid arthritis with symptoms or signs of active joint inflammation
11. Pregnancy or nursing. In order to avoid pregnancy, women had to be postmenopausal, surgically sterile, or women of child bearing potential must have used one of the following contraceptives during the whole study period and after the study had ended for at least 5 times plasma biological half-life of the investigational medicinal product: contraceptive pills, intrauterine devices, contraceptive injections (prolonged-release gestagen), subdermal implantation, vaginal ring, and transdermal patches
12. Extensive active bleeding necessitating blood transfusion
13. Planned elective surgery during the study
14. Participation in any other clinical study within 3 months prior to screening
15. Intolerance to oral iron treatment
16. Untreated vitamin $B_{12}$ or folate deficiency
17. Other IV or oral iron treatment or blood transfusion within 4 weeks prior to the screening
18. Treated with erythropoietin within 8 weeks prior to the screening
19. Diagnosis of Hepatitis B and/or C, confirmed by appropriate laboratory test
20. Any other medical condition that, in the opinion of Investigator, may cause the subject to be unsuitable for the completion of the study or placed the subject at potential risk from being in the study, e.g. uncontrolled hypertension, unstable ischemic heart disease, or uncontrolled diabetes mellitus
21. History of immunocompromise, including positive human immunodeficiency virus test results

**Test product, dose and mode of administration, batch/lot number**

Monofer® was the test product in this study. The lot numbers used were 09101601 and 09082601 for 100 mg/mL in 10 mL ampoule and 10100701 and 11121201 for 100 mg/mL in 5 mL vial.

Full iron replacement dose with iron isomaltoside 1000 was calculated based on the following Ganzoni formula:

Total iron dose (mg) = body weight (kg) x targeted Hb – actual Hb (g/dL) x 2.4 + depot iron (mg) where

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Depot iron: 500 mg

Targeted Hb: 13.0 g/dL

This calculation was transformed into a simple dosing regimen by means of a dosing table (Appendix 1 of protocol version 1.0 dated 18 June 2009) which was followed in each case. Drug dosage and mode of administration were as follows:

Group A1: Iron isomaltoside 1000 – IV infusion

The full iron replacement dose of iron isomaltoside 1000 was administered as IV infusion of maximum 1000 mg* iron isomaltoside 1000 as single doses over 15 min. The full iron replacement was achieved by 1 or up to 2 doses at weekly intervals.

Group A2: Iron isomaltoside 1000 – bolus IV injection

The full iron replacement dose was administered as IV bolus injections of 500 mg iron isomaltoside 1000 over 2 min once weekly until full replacement dose was achieved. In some cases, the remaining dose on the last dosing day was 250 mg. For e.g., if the full replacement dose was 1250 mg, on visit 4 the remaining 250 mg was administered.

* The maximum dose per infusion was 1000 mg for subjects with a weight > 45 kg, 750 mg for subjects with a weight between 35 and 45 kg, and 500 mg for subjects with a weight < 35 kg.

**Duration of treatment**

Duration of treatment varied according to the treatment group. Subjects randomised to group A1 were treated with 1or 2 doses in total with 1 week between the doses. Subjects randomised to group A2 were treated 1-4 times during 3 weeks, and subjects randomised to group B were treated daily for 8 weeks.

**Reference therapy, dose and mode of administration, lot number**

Ferro Duretter® was the reference therapy that was administered orally at a dose of 100 mg elementary iron twice a day (200 mg daily) for 8 weeks. The lot numbers were AD903B and AD013A.

**Statistical methods**

Sample size calculations

The sample size calculation was based on absolute change in Hb from baseline to week 8. The non-inferiority margin was set as 0.5 g/dL. This margin was in line with previous studies and was regarded as clinically relevant. A two-sided significance level of 5 % was used and the power was set to 80 %.

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The table below shows the number of subjects required per randomised treatment group in order to demonstrate non-inferiority with a margin of 0.5 g/dL when using a 2:1 randomisation for different Standard Deviations (SDs).

| SD of Change in Hb (g/dL) | Number of Subjects per Group (A/B) |
|---|---|
| 1.25 | 150/75 |
| 1.5 | 214/107 |
| 1.75 | 290/145 |
| 2.0 | 380/190 |
| 2.25 | 480/240 |

Based on available literature and previous studies with iron isomaltoside 1000, the SD in change in Hb was assumed to be approximately 1.5 g/dL. On the basis of this, a total of 321 subjects were to be included in the efficacy analyses (i.e. provided post-randomisation Hb measurements).

The primary analysis was to assess non-inferiority. In case the 95 % confidence interval (CI) lay entirely above 0, this was evidence of superiority in terms of statistical significance at the 5 % level. In that case, the *p*-value associated with a test of superiority was calculated and evaluated whether this was sufficiently small to reject the hypothesis of no difference.

Drop-outs were expected during the study. As the study was designed to demonstrate non-inferiority, both analyses of the Full Analysis Set (FAS) and the Per Protocol (PP) analysis set would have led to similar conclusions. Therefore analyses for both analysis sets were powered properly. With approximately 10 % (anticipated) of subject population expected to have major protocol violations, a total of 350 subjects were to be randomised.

<u>Key elements of the analysis plan</u>

The primary efficacy data was calculated using sample number, mean, SD, minimum, maximum, and 95 % CI. The analysis of co-variance mixed model with repeated measures was used to compare the average change in Hb concentration from baseline to end of study with the use of treatment, visit, treatment*visit interactions, country, and stratum (parenteral iron (Yes/No) as factors and baseline values as covariates). The visit*treatment estimate at week 8 was used as estimate model. All tests were two-tailed and significance level was 0.05.

Summary tables and descriptive statistics were done for demographics, efficacy, and safety variable. Comparison to baseline analyses of treatment effects with relevant test are described in the statistical analysis plan.

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**Baseline characteristics and summary of efficacy results**

***Baseline characteristics***

Of the 327 subjects in the FAS, 63.0 % were women and 37.0 % were men, 61.2 % were Asians and 37.6 % were Europeans, and 92.7 % subjects were non-smokers. The mean age of the subject population was 37 years (SD: 12 years), weight was 57 kg (SD: 13 kg), height was 163 cms (SD: 9 cms), and BMI was 21 kg/m$^2$ (SD: 4 kg/m$^2$). In terms of diagnosis of IBD, 103 (31.5 %) subjects (group A: 66; group B: 37) were diagnosed with Crohn's disease and 224 subjects (68.5 %) (group A: 153; group B: 71) with ulcerative colitis. Ulerative colitis was more common than Crohn´s disease in the Asian population whereas Crohn´s disease was more common than ulcerative colitis in the European population. The mean duration of illness for Crohn's disease was 10 years (SD: 9 years, range: 0.01:40 years) and for ulcerative colitis it was 3 years (SD: 5 years, range: 0.00:32 years).

The mean cumulative dose of iron isomaltoside 1000 administered to the subjects in group A1 and A2 in the safety analysis set were 885 mg (SD: 238 mg, range: 195:1500) and 883 mg (SD: 296 mg, range: 350:2500), respectively. A total of 129 infusions of iron isomaltoside 1000 were administered to 110 subjects in the group A1 and 227 bolus injections of iron isomaltoside 1000 were given to 113 subjects in group A2. Oral iron was administered as 200 mg iron sulphate daily for 8 weeks (11200 mg in total for subjects completing 8 weeks oral treatment).

***Increase in Haemoglobin***

Non-inferiority could not be statistically demonstrated on the primary endpoint which was comparison of change in Hb concentration from baseline to week 8 between group A and B (FAS: $p = 0.0945$; PP: $p = 0.0355$). The present study demonstrated an increase in Hb concentration from a mean (SD) of 9.64 (1.65) g/dL at baseline to 12.23 (1.33) g/dL at week 8 in subjects treated with iron isomaltoside 1000 and an increase from 9.61 (1.82) g/dL at baseline to 12.59 (1.91) g/dL at week 8 in subjects treated with oral iron sulphate. Oral iron sulphate demonstrated a trend to a higher increase from baseline in Hb at week 8 in this study (3.04 g/dL versus 2.58 g/dL) and in particular Asian subjects had a pronounced response to oral iron sulphate. No statistical differences in efficacy between group A1 and A2 as compared to group B was found on the primary endpoint.

There was no statistically significant difference in the increase in Hb from baseline to week 2 and 4 between group A and group B. Similar results were obtained when group A was divided into group A1 and A2.

Within the IV arm (group A) an indication of a dose relationship was found. Iron isomaltoside 1000 was found to be more efficacious with cumulative doses of ≥ 1000 mg in both the overall subject population as well as in the European population.

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***Number of Responders***

In the present study, subjects achieving target limits of Hb (13-18 g/dL in men and 12-16 g/dL in women), *s*-ferritin (100-800 µg/L), TSAT (20-50 %), and a change in Hb concentration > 1.0 g/dL were significantly higher in subjects in group A at week 2 ($p < 0.0001$) and at week 4 ($p = 0.0227$) compared to group B. At week 8, there was no statistically significant difference in the number of responders in group A compared to group B.

Though, non-inferiority of iron isomaltoside 1000 to iron sulphate could not be established, the efficacy of iron isomaltoside 1000 was supported by the response rate of Hb increase > 2 g/dL which was observed in 64 % of the subjects treated with IV iron (group A) compared to 61 % in subjects treated with oral iron (group B). Low baseline Hb seemed to be a predictor for response as per this criteria, but further studies and analyses are needed in order to evaluate potential predictors for response versus non-response.

***Change in S-iron, S-ferritin, and TSAT***

The mean (SD) change in *s*-iron concentration from baseline to week 8 was significantly lower in group A compared to group B ($p < 0.0001$).

Treatment with iron isomaltoside 1000 resulted in a better response in terms of *s*-ferritin concentration as compared to treatment with oral iron sulphate. Subjects treated with iron isomaltoside 1000 had a significantly higher increase in *s*-ferritin concentration from baseline to week 1, 2, 4, and 8 in comparison to subjects treated with oral iron sulphate.

An increase in TSAT was observed with treatment with both iron isomaltoside 1000 and iron sulphate. However, the change in TSAT from baseline to week 8 was significantly lower in group A compared to group B.

***Number of Subjects who Discontinued Study because of Lack of Response or Intolerance to Investigational Drugs***

None of the subjects in group A discontinued the study due to lack of response or intolerance to iron isomaltoside 1000. In group B, 3.7 % of the subjects discontinued the study due to lack of response or intolerance to iron sulphate. The difference in the number of subjects between group A and B was not statistically significant.

***Change in Total Quality of Life Score***

An increase in QoL score from baseline to week 4 and 8 was observed across both treatment groups. There was no significant difference in the increase in the QoL score from baseline to week 4 and week 8 between the treatment groups.

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***Change in Restless Legs Syndrome Score***

RLS data were obtained from 125 subjects in group A and none in group B at baseline in the safety analysis set. A total of 7 subjects had definite RLS, whereas the remaining 118 subjects did not have any RLS symptoms. The CH-RLS score decreased from the baseline to week 8 in group A thereby showing improvement in RLS symptoms. Of the 7 subjects that had definite RLS status at baseline, 4 (57.1 %) subjects had no RLS symptoms by EOS.

**Summary of safety results**

The safety profile of iron isomaltoside 1000 in this study showed no differences in safety between group A and B. Iron isomaltoside 1000 was administered in single doses up to 1000 mg as infusions in group A1 and 500 mg bolus injections in group A2. The cumulative doses were ranging from 195 mg to to 1500 mg in group A1 and 350 mg to 2500 mg in group A2. The average cumulative dose of iron isomaltoside 1000 administered to the subjects in group A1 and A2 were 885 mg (SD: 237 mg) and 883 mg (SD: 296 mg), respectively. The average duration of infusion in group A1 at baseline was 19 min (SD: 12 min, range: 2:94) at baseline.

Overall, 121 subjects (group A: 85 (38.1 %); group B: 36 (33.0 %)) reported a total of 202 TEAEs (group A: 146; group B: 56) during the study. Of these 202 TEAEs, 9 were serious and 193 were non-serious. The 9 SAEs were reported in a total of 8 subjects (3.6 %) in group A.

The number of mild and moderate AEs was comparable between the treatment groups. Severe AEs (n = 5) were only reported in group A for a total of 4 (1.8 %) subjects. A total of 6 subjects (3 subjects each in group A and group B) who had been treated with the study drug discontinued from the study due to 8 TEAEs (group A: 5; group B: 3).

A total of 54 AEs (group A: 42 (28.77 %); group B: 12 (21.43 %)) were considered related to study treatment and were reported in 42 subjects (group A: 31 (13.9 %) subjects; group B: 11 (10.1 %) subjects). The remaining AEs were not considered related to study treatment. Related AEs reported in 2 subjects or more were flushing (6 subjects), hypersensitivity and diarrhoea (3 subjects), increase of hepatic enzymes (4 subjects), hypotension, hypertension, urticaria, headache, abdominal pain, and nausea (2 subjects) in group A and diarrhoea (4 subjects) and constipation (2 subjects) in group B. In group A, flushing, elevation of hepatic enzymes, and diarrhoea were reported as related AEs in subjects receiving < 1000 mg as well as ≥ 1000 mg iron isomaltoside 1000. The transient increase in hepatic enzymes in 4 subjects was not above the 3 times upper level cut off for hepatic enzymes and the 4 hypersensitivity reactions were non-serious.

The majority of TEAEs were recovered without sequelae (group A: 117 (80.1 %); group B: 40 (71.4 %)), 39 TEAEs (group A: 23 (15.8 %); group B: 16 (28.6 %)) were ongoing at the time and follow-up was not necessary, and 1 (0.7 %) TEAE in group A was recovered with sequelae. Two (1.4 %) TEAEs (respiratory distress and hypotension) led to fatal outcome in a subject (0.9 %)

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treated with iron isomaltoside 1000 who died during the study due to causes unrelated to study treatment.

A total of 9 SAEs occurred of which 8 were not related to the study drug. A single SAE of grand mal seizure was probable related to iron isomaltoside 1000. The event resolved spontaneously and the subject was withdrawn. The 3 months follow-up did not show any re-occurrence of seizure and the outcome was recovered without any sequelae. All other SAEs were considered unlikely or not related to the study drug by the Investigator.

No dose relationship was seen with the frequency of AEs, SAEs, or ADRs.

At all visits, the haematological and biochemistry parameters and vital signs were comparable between the treatment groups. Analysis of hypophosphataemia (defined as < 2 mg/dL) associated with IV iron showed that the incidence of hypophosphataemia increased from < 1 % at baseline to 7 % at week 2, and then decreased to 1 % at EOS in group A.

Abnormal clinically significant physical examination findings which were not present at screening but were observed at EOS were recorded as AEs. Clinically significant abnormalities of alopecia and pigmentation of the face observed in 1 subject each in group A were considered possible related to iron isomaltoside 1000 and the rest were unlikely or not related to the study drug. The outcome for majority of these clinically significant abnormalities in both the treatment groups was ongoing with follow-up not necessary.

No clinically significant abnormality was observed in the ECG at baseline or EOS. In all treatment groups, folic acid, mesalazine, prednisolone, pantoprazole and azathioprine were the commonly used concomitant medications by > 10 % of the subject population.

No significant difference was observed in safety between group A1 and group A2.

**Conclusion**

The present study demonstrated an increase in Hb concentration from a mean (SD) of 9.64 (1.65) g/dL at baseline to 12.23 (1.33) g/dL at week 8 in subjects treated with iron isomaltoside 1000 and an increase from 9.61 (1.82) g/dL at baseline to 12.59 (1.91) g/dL at week 8 in subjects treated with oral iron sulphate. Oral iron sulphate demonstrated a trend to a higher increase from baseline in Hb at week 8 in this study (3.04 g/dL versus 2.58 g/dL) and in particular Asian subjects had a pronounced response to oral iron sulphate. Hence, non-inferiority could not be statistically demonstrated on the primary endpoint. However, the present study reported that treatment with iron isomaltoside 1000 was safe and effective in increasing Hb (64 % of subjects had an increase of > 2 g/dL). In particular, a higher increase in Hb concentration was observed with higher dosing of 1000 mg or more without compromising safety. Hence, in IBD subjects the Ganzoni formula

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seem to underestimate the IV iron dose needed when calculated with a target Hb of 13 g/dL and iron stores at 500 mg.

Both single doses up to 1000 mg infusions of iron isomaltoside 1000 over 15 min and bolus injections up to 500 mg over 2 min without a test dose were well tolerated.

The protocol excluded subjects with known intolerance to oral iron and with severe disease activity. Therefore, selection bias for iron-tolerant subjects may have played an important role interpreting the oral response in this study.

**Date of the report**

05 February 2016