SYNOPSIS

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Name of active ingredient Iron isomaltoside 1000		

Title of study

An open-label, multi-centre, non-randomised extension study to assess the ability to maintain a stable haemoglobin and to assess safety of iron isomaltoside 1000 (Monofer®) in subjects with inflammatory bowel disease

Investigators

The list of investigators is presented in the Appendix 16.1.4.

Study centres

The study was initiated at [redacted]

Publication (reference)

The study design, dosing, and safety status of P-Monofer-IBD-01-Extension was presented as an oral presentation at the European Crohn's and Colitis Organisation (ECCO) conference in Vienna, February 2013.

Studied period

First subject first visit: 07 June 2011

Last subject last visit: 11 July 2013

Phase of development

Phase III

Study design

The study was a prospective, open-label, multi-centre, non-randomised, observational extension study of the lead-in study in inflammatory bowel disease (IBD) subjects with iron deficiency anaemia (IDA) (P-Monofer-IBD-01). The enrolment period of the study was 6 months (June-November 2011). The study duration for the individual subject was approximately 12 months and each subject attended 5 visits (one screening/baseline visit (visit 1), three treatment/follow-up visits (visit 2-4), and one end of study (EOS) visit (visit 5)).

Objectives

Primary efficacy objectives

- To assess the long-term efficacy of iron isomaltoside 1000 by means of the ability to

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maintain stable haemoglobin (Hb) (defined as Hb ≥ 12.0 g/dL) in subjects with Hb ≥ 12.0 g/dL at baseline of the extension study

- To assess the ability to achieve stable Hb (Hb ≥ 12.0 g/dL) at month 3 visit of the extension study and then to maintain the stable Hb thereafter in subjects with Hb < 12.0 g/dL at baseline of the extension study

Secondary efficacy objectives

- To assess the dosage and frequency of additional iron isomaltoside 1000, if administered
- To assess the change in other relevant biochemical parameters (serum (*s*)-iron, *s*-ferritin, total iron binding capacity (TIBC), and transferrin saturation (TSAT))
- To assess quality of life (QoL) by inflammatory bowel disease questionnaire (IBDQ)
- To assess the change in restless leg syndrome (RLS) score by Cambridge-Hopkins RLS questionnaire (CH-RLSq) in subjects with RLS symptoms in the lead-in study
- To assess disease activity status using Harvey-Bradshaw Index for Crohn's disease or partial Mayo score (excluding endoscopy sub-score) for ulcerative colitis
- To assess the change in platelet count

Safety objective

- To assess the long-term safety of iron isomaltoside 1000 maintenance

Endpoints

Primary efficacy endpoints

- Number of subjects (with Hb ≥ 12.0 g/dL at baseline of the extension study) who maintained stable Hb (defined as Hb ≥ 12.0 g/dL) at all visits of the extension study
- Number of subjects (with Hb ≥ 12.0 g/dL at month 3 visit of the extension study) who maintained stable Hb (defined as Hb ≥ 12.0 g/dL) at all visits from month 3 visit of the extension study in subjects with Hb < 12.0 g/dL at baseline of the extension study*

* The formulation of this endpoint in the protocol was not entirely clear. The subjects only needed to have a Hb < 12.0 g/dL at baseline and not a Hb ≥ 12.0 g/dL at month 3 in order to be included in the endpoint. Thus, the endpoint evaluated the number of subjects who maintained stable Hb (defined as Hb ≥ 12.0 g/dL) at all visits from month 3 visit of the extension study in subjects with Hb < 12.0 g/dL at baseline of the extension study.

Exploratory efficacy endpoints

- Time to Hb < 12.0 g/dL in subjects with baseline Hb ≥ 12 g/dL or reaching Hb ≥ 12.0

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g/dL during the study

- Time (from start of extension study) to change (from baseline in lead-in study) in Hb < 2 g/dL for responders (subjects with change in Hb ≥ 2.0 g/dL at any visit in the lead-in study)

Secondary efficacy endpoints

- Number of subjects who achieved stable Hb (Hb ≥ 12.0 g/dL) at any single visit
- Number of consecutive visits for which stable Hb (Hb ≥ 12.0 g/dL) was maintained
- Dosage of iron isomaltoside 1000 re-administered, if required
- Frequency of additional dosing of iron isomaltoside 1000, if required
- Change in concentrations of *s*-iron, *s*-ferritin, TIBC, and TSAT from baseline to EOS (visit 5) of the extension study
- Change in total QoL score (IBDQ score) from baseline to month 6 and EOS (visit 5) of the extension study
- Change in RLS symptoms by CH-RLSq score (in subjects with RLS symptoms in the lead-in study) from baseline to month 6 and EOS of the extension study
- Change in disease activity status using Harvey-Bradshaw Index for Crohn's disease, or partial Mayo score (excluding endoscopy sub-score) for ulcerative colitis from baseline to month 6 and EOS (visit 5) of the extension study
- Number of subjects who discontinued study because of lack of response or intolerance to investigational drug
- Change in platelet count from baseline to month 6 and EOS (visit 5) of the extension study

Safety endpoint

- Number of subjects who experienced any adverse drug reaction (ADR) including any suspected unexpected serious adverse reaction (SUSAR)

Efficacy assessments

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

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- TIBC
- TSAT
- Change in total QoL score (IBDQ score)
- Change in RLS symptoms (CH-RLSq)
- Change in disease activity

Safety assessments

- Adverse events (AEs)
- Safety laboratory variables
    - Haematology
        - Complete blood count (red blood cell count, white blood cell count including differential count, mean corpuscular volume, mean corpuscular Hb, mean corpuscular Hb concentration, haematocrit, and platelet count)
    - Biochemistry
        - C-reactive protein
        - *S*-sodium, *s*-potassium, *s*-calcium, *s*-phosphate, *s*-urea, *s*-creatinine, *s*-albumin, *s*-globulin, and albumin:globulin ratio
        - *S*-bilirubin
        - Aspartate aminotransferase
        - Alanine aminotransferase
- Physical examination
- Vital signs (systolic blood pressure (BP), diastolic BP, pulse rate, and electrocardiogram)
- Weight

Study population

39 subjects with a diagnosis of IBD along with IDA were screened and enrolled in the study.

Subjects from the lead-in study (P-Monofer-IBD-01) were offered to participate in the extension study and had to fulfil the following eligibility criteria in order to be included.

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Inclusion criteria

1. Completed the lead-in study or discontinued from the lead-in study due to intolerance to oral iron
2. Life expectancy beyond 18 months by investigator's judgement
3. Willingness to participate after signing informed consent

Exclusion criteria

1. Discontinuation from the lead-in study (except for due to intolerance to oral therapy)
2. Any major protocol deviation in the lead-in study
3. Pregnancy and nursing (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 (5 days): contraceptive pills, intrauterine devices, contraceptive injections (prolonged-release gestagen), subdermal implantation, vaginal ring, and transdermal patches)
4. Any other medical condition that, in the opinion of the investigator, may have caused the subject to be unsuitable for completion of the study or has placed the subject at potential risk from being in the study
5. Subjects with a Harvey-Bradshaw Index > 8 or partial Mayo score (excluding endoscopy sub-score) > 6 at EOS (visit 7) of the lead-in study

Test product, dose and mode of administration, batch number

Monofer® (iron isomaltoside 1000) was the test product in this study. The lot number used was 11041401.

No fixed interval of drug administration was planned for the study since the extension study was primarily planned to observe the long-term efficacy and safety of iron isomaltoside 1000 in subjects on treatment in the lead-in study. For subjects with Hb < 12.0 g/dL, TSAT < 20 %, and *s*-ferritin < 500 µg/L at any single visit of the extension study, iron isomaltoside 1000 was administered as a single dose infusion (loading dose) according to the following loading dosing regimen, considering the Hb levels and weight at the extension study baseline*:

Haemoglobin	**Body weight < 70 kg**	**Body weight ≥ 70 kg**
10.0 g/dL ≤ Hb < 12.0 g/dL	1000 mg	1500 mg
Hb < 10.0 g/dL	1500 mg	2000 mg

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[redacted]

For subjects with a stable Hb (Hb ≥ 12.0 g/dL), TSAT < 20 %, and *s*-ferritin < 500 µg/L at any single extension study visit (except EOS (visit 5) of the extension study), iron isomaltoside 1000 was administered as a maintenance dose according to the following fixed maintenance dosing regimen:

Iron status	**Body weight < 70 kg**	**Body weight ≥ 70 kg**
TSAT < 20 % and 100 µg/L < *s*-ferritin < 500 µg/L	500 mg	1000 mg
TSAT < 20 % and *s*-ferritin ≤ 100 µg/L	1000 mg	1500 mg

Duration of treatment

Subjects received a single dose infusion of iron isomaltoside 1000 over approximately 15 min. No test dose was applied. The infusion was prepared by diluting iron isomaltoside 1000 in 100 mL normal saline (0.9 % sodium chloride).

Reference therapy, dose and mode of administration, batch number

No reference therapy was used in this study.

Statistical methods

Sample size calculation

No sample size calculations were performed. Based on the assumption that all subjects from the lead-in study could be enrolled into the extension study, irrespective of the treatment provided in the lead-in study, it was anticipated to include approximately 50 subjects in the study.

Key elements of the analysis plan

All statistical tests were carried out as two-sided on a 5 % level of significance unless otherwise stated. Continuous variables were summarised using descriptive statistics (number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum). Categorical data were summarised with number of exposed subjects and number with percentage of observations in various categories of the endpoints.

Demographic variables that were measured on a continuous scale like age of the subject were summarised using descriptive statistics and the categorical variables like gender were summarised using frequencies and percentages. Screening medical history was tabulated by body system and summarised by using frequencies and percentages.

Primary analyses

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The number of subjects who achieved a stable Hb (Hb ≥ 12.0 g/dL) at any extension study visit was summarised descriptively with frequency and percentage of subjects for categorical data. In addition to the descriptive displays, subjects with missing observations were censored and Kaplan-Meier methodology was used to estimate the probability for maintaining a stable Hb (Hb ≥ 12.0 g/dL) for 1 year. Subgroups according to the lead-in treatment were compared. There were two subgroups (i) subjects with Hb ≥ 12.0 g/dL at baseline, (ii) subjects with Hb < 12.0 g/dL at baseline. Kaplan-Meier analysis was performed on these subgroups only as primary endpoint analysis.

Exploratory analyses were further conducted on the primary endpoints involving two subgroups (i) subjects with Hb ≥ 12.0 g/dL at baseline or at any visit, (ii) subjects with change in Hb ≥ 2.0 g/dL at any visit during the lead-in study. Kaplan-Meier plot was used to estimate the probability for maintaining stable Hb (Hb ≥ 12.0 g/dL) for 1 year and for maintaining a change in Hb ≥ 2.0 g/dL for 1 year.

Secondary analyses

The number of subjects who achieved Hb ≥ 12.0 g/dL at any single visit was summarised descriptively with frequency and percentage of subjects. Number of visits for which Hb ≥ 12.0 g/dL was maintained was summarised descriptively. Dosage and frequency of additional dosing of iron isomaltoside 1000, concentrations of *s*-iron, *s*-ferritin, TIBC, and TSAT at each visit of the study were summarised. Paired t-test was used to compare mean concentrations at baseline and 12 months (EOS) at 5 % level of significance. The changes in total QoL scores, CH-RLSq scores, disease activity status using Harvey-Bradshaw Index for Crohn's disease, or partial Mayo score for ulcerative colitis, and platelet count were summarised and compared using paired t-test from baseline to 6 months and 12 months (EOS). Number of subjects who discontinued the study because of lack of response or intolerance to investigational product were summarised descriptively with frequency and percentage of subjects.

Longitudinal response profile of primary, secondary, and other continuous endpoints were displayed by plotting means (± 95 % confidence interval) of treatment using a line/bar chart over study visits/period.

Safety analyses

All safety parameters, including AEs, laboratory safety variables, physical examination, vital signs, and weight were presented by descriptive statistics. AEs were collected and evaluated for relatedness, severity, seriousness, and expectedness. AEs were coded by system organ class and preferred term using the latest version 16.0 of medical dictionary for drug regulatory affairs body system and tabulated by indicating number and percentage of subjects and number of events. The number of subjects who experienced any ADR including any SUSAR was summarised. Concomitant medications, concurrent illnesses, and medical history were

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listed by subject.

Summary of efficacy results

39 subjects were enrolled in this extension study where 35 were included in the full analysis set (FAS), 25 in the per protocol (PP) analysis set, and all 39 subjects were included in the safety population. 4 subjects were excluded from the FAS as 3 subjects withdrew consent and 1 subject received another investigational drug concurrently. Both FAS and PP datasets were evaluated for analyses of efficacy endpoints. In the FAS, the mean (SD) Hb concentration was 12.29 (1.45) g/dL at baseline, 12.79 (1.62) g/dL at 3 months, 12.77 (1.60) g/dL at 6 months, 12.88 (1.35) g/dL at 9 months and 12.94 (1.58) g/dL at 12 months (EOS). The average change in Hb concentration from baseline to 12 months was 0.69 g/dL.

23 of 35 subjects in the FAS had a Hb ≥ 12.0 g/dL at baseline and the remaining 12 had a Hb < 12.0 g/dL at baseline. 16 of 25 subjects in the PP analysis set had a Hb ≥ 12.0 g/dL at baseline and the remaining 9 had a Hb < 12.0 g/dL at baseline.

Maintenance of stable haemoglobin ≥ 12.0 g/dL in subjects with haemoglobin ≥ 12.0 g/dL at baseline

Out of 23 (65.7 %) subjects with Hb ≥ 12.0 g/dL at baseline, 15 subjects had received iron isomaltoside 1000 (infusion: 8; bolus: 7) and 8 subjects had received oral iron sulphate in the lead-in study. Of these subjects, 8 (4: IV iron isomaltoside 1000 in lead-in study, 4: oral iron sulphate in lead-in study) maintained a stable Hb (Hb ≥ 12.0 g/dL) at all follow-up visits, 6 subjects had a Hb < 12.0 g/dL at one or more follow-up visit(s), and the remaining 9 subjects either withdrew consent, were lost to follow-up, dropped out, had an AE, or had a missed visit without experiencing a Hb value < 12.0 g/dL. The crude last observation carried forward (LOCF) estimate was 17/23 (74 %) of subjects with Hb ≥ 12.0 g/dL at baseline were able to maintain Hb ≥ 12.0 g/dL during the study.

The Kaplan-Meier plot of time to a Hb < 12.0 g/dL estimated that 17 of the 23 subjects with a Hb ≥ 12.0 g/dL at baseline would maintain a Hb ≥ 12.0 g/dL up to 1 year with a probability of 0.638. This was in line with the crude LOCF estimate.

Achievement and maintenance of stable haemoglobin ≥ 12.0 g/dL in subjects with haemoglobin < 12.0 g/dL at baseline

The primary analysis also included assessment of achievement and maintenance of a stable Hb (Hb ≥ 12.0 g/dL) at all visits after baseline in subjects with a Hb < 12.0 g/dL at baseline. Out of 12 (34.3 %) subjects with a Hb < 12.0 g/dL at baseline, 9 subjects had received iron isomaltoside 1000 (infusion: 5; bolus: 4) and 3 subjects had received oral iron sulphate in the lead-in study. Of these subjects, 3 (2: IV iron isomaltoside 1000 in lead-in study, 1: oral iron sulphate in lead-in study) maintained a stable Hb (Hb ≥ 12.0 g/dL) at all follow-up visits, 8

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subjects had a Hb < 12.0 g/dL at one or more follow-up visit(s), and 1 subject withdrew consent. The crude LOCF estimate was 4/12 (33.3 %) of subjects with Hb < 12.0 g/dL at baseline were able to maintain Hb ≥ 12.0 g/dL during the study.

The probability of maintaining a Hb ≥ 12.0 g/dL at 1 year in subjects with Hb < 12.0 g/dL at baseline was 0.313 which was predominantly due to subjects not achieving Hb ≥ 12.0 g/dL at the month 3 visit. The LOCF estimate was in line with the Kaplan-Meier estimate.

Achievement and maintenance of stable haemoglobin ≥ 12.0 g/dL in subjects with baseline Hb ≥ 12 g/dL or reaching Hb ≥ 12.0 g/dL during the study

Out of 32 subjects with a Hb ≥ 12.0 g/dL at baseline or any follow-up visit, 24 (75 %) subjects maintained a Hb ≥ 12.0 g/dL at all study visits and 8 (25 %) had a Hb < 12.0 g/dL at one or more follow up visit(s) during the study. The Kaplan-Meier plot of time to occurrence of Hb < 12.0 g/dL for subjects with baseline Hb ≥ 12 g/dL or reaching Hb ≥ 12.0 g/dL during the study estimated that 24 subjects would maintain a Hb ≥ 12.0 g/dL at 1 year with a probability of 0.628.

Achievement and maintenance of change in Hb ≥ 2.0 g/dL in subjects that had a response of Hb ≥ 2.0 g/dL at any visit in the lead-in study

Out of 23 subjects that had a response of Hb ≥ 2.0 g/dL at any visit in the lead-in study, 17 out of 35 (48.6 %) subjects had a change in Hb ≥ 2.0 g/dL at any visit and 6 out of 35 (17.1 %) subjects had a change in Hb < 2.0 g/dL during the study. The Kaplan-Meier plot of time to a change in Hb < 2.0 g/dL estimated that 17 of the 23 subjects would maintain a change in Hb ≥ 2.0 g/dL up to 1 year with a probability of 0.707.

Number of subjects who achieved haemoglobin ≥ 12.0 g/dL at any single visit

Overall, 23/35 (65.7 %) subjects at baseline, 26/34 (76.5 %) subjects at 3 months, 20/27 (74.1 %) subjects at 6 months, 19/25 (76.0 %) subjects at 9 months, and 20/26 (76.9 %) subjects at 12 months (EOS) had Hb ≥ 12.0 g/dL.

Out of 23 subjects with Hb ≥ 12.0 g/dL at baseline, 21/22 (95.5 %) subjects at 3 months, 12/15 (80.0 %) subjects at 6 months, 12/14 (85.7 %) subjects at 9 months, and 13/16 (81.3 %) subjects at 12 months (EOS) achieved Hb ≥ 12.0 g/dL. The proportion of subjects with Hb ≥ 12.0 g/dL was similar between follow-up visits.

Out of 12 subjects with Hb < 12.0 g/dL at baseline, 5/12 (41.7 %) subjects at 3 months, 8/12 (66.7 %) subjects at 6 months, 7/11 (63.6 %) subjects at 9 months, and 7/10 (70.0 %) subjects at 12 months (EOS) achieved Hb ≥ 12.0 g/dL. The proportion of subjects with Hb ≥ 12.0 g/dL increased from baseline to 12 months (EOS).

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Number of consecutive visits with stable haemoglobin maintained

Of the 35 subjects in the FAS, 33 (94.3 %) had a Hb ≥ 12.0 g/dL at any single visit, 22 out of 27 (81.5 %) subjects had a Hb ≥ 12.0 g/dL at any 2 consecutive visits, 15 out of 25 (60 %) subjects had a Hb ≥ 12.0 g/dL at any 3 consecutive visits, and 11 out of 24 (45.8 %) subjects had a Hb ≥ 12.0 g/dL at any 4 consecutive visits (including baseline).

Dosage of iron isomaltoside 1000 re-administered

34 of 39 enrolled subjects were re-dosed with iron isomaltoside 1000 during the study. Of these, 27 subjects were re-dosed at baseline, 16 subjects at 3 months, 13 subjects at 6 months, and 12 subjects were re-dosed at 9 months. It is to be noted, that 6 of 27 re-dosed subjects at baseline were re-dosed at 3, 6, and 9 months. A higher proportion of subjects were re-dosed as per the maintenance dosing regimen based on Hb ≥ 12.0 g/dL, TSAT < 20 %, and *s*-ferritin < 500 µg/L in comparison to the loading dosing regimen based on Hb < 12.0 g/dL, TSAT < 20 %, and *s*-ferritin < 500 µg/L at baseline (51.85 % versus 44.44 %), 3 months (56.25 % versus 37.5 %), and at 9 months (66.67 % versus 33.33 %). At 6 months, 46.15 % of the subjects were re-dosed as per the loading dosing and per the maintenance dosing regimen.

The majority of the subjects were re-dosed as per the scheduled dose at each visit. 7.41 % of the subjects at baseline and 12.5 % of the subjects at 3 months were administered either a higher or lower dose than the scheduled dose. At 6 months 7.69 % of the subjects and 8.33 % of the subjects at 9 months were administered higher dose than the scheduled dose and none of the subjects were administered a dose lower than the scheduled dose at these visits. Overall, the mean cumulative dose administered was 2192 mg (SD: 1580, range: 30:7000 mg) and the median single dose across visits was 1000 mg. The mean (SD) dose administered under the standardized loading dosing regimen ranged from 1250 (261) mg at baseline to 1417 (492) mg at 6 months. The mean (SD) dose administered under the maintenance dosing regimen ranged from 837 (426) mg at 3 months to 1107 (488) mg at baseline visit. The mean dose of iron isomaltoside 1000 was numerically higher under the standardized loading dosing regimen as compared to maintenance dosing regimen across all visits.

1000 mg of iron isomaltoside 1000 was administered to 11/27 subjects at baseline, 10/16 subjects at 3 months, 7/13 subjects at 6 months, and 4/12 subjects at 9 months while 12/27 subjects at baseline, 3/16 subjects at 3 months, 4/13 subjects at 6 months, and 4/12 subjects at 9 months received > 1000 mg of iron isomaltoside 1000. The mean single dose of iron isomaltoside 1000 re-administered at different visits was comparable (baseline: 1167 mg, 3 months: 1002 mg, 6 months: 1154 mg, 9 months: 1000 mg).

Frequency of additional dosing of iron isomaltoside 1000

Out of 34 re-dosed subjects, 15 were dosed once, 10 were dosed twice, 3 were dosed thrice,

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and 6 subjects were dosed four times. Out of the subjects that were dosed once, 6 out of the 7 subjects, who were followed for all visits till month 12, had Hb ≥ 12.0 g/dL at month 12. Out of the subjects that were dosed twice 9 subjects of 10 subjects, who were followed for all visits till month 12, had Hb ≥ 12.0 g/dL at month 12. Out of the subjects that were dosed thrice, all 3 subjects who were followed for all visits till month 12 had Hb ≥ 12.0 g/dL at month 12. Out of the subjects that were dosed four times 1 subject out of 5 subjects who were followed for all visits till month 12 had Hb ≥ 12.0 g/dL at month 12.

Change in concentrations of serum iron, serum ferritin, total iron binding concentration, and transferrin saturation from baseline to end of study

A rapid increase in *s*-iron, *s*-ferritin, and TSAT concentration was observed from baseline to 3 months followed by a gradual increase at 6 months, 9 months, and 12 months (EOS). There was a statistical significant increase in *s*-iron ($p = 0.0029$), *s*-ferritin ($p < 0.0001$), and TSAT ($p = 0.0003$) concentration from baseline to 12 months (EOS). The TIBC concentration decreased from baseline to 3 months, 6 months, 9 months, and 12 months (EOS) but the decrease was not statistical significant ($p = 0.2116$).

Change in total quality of life score

There was an increase in total QoL score from baseline to 6 months and 12 months (EOS), however, the increase was not statistical significant (6 months: $p = 0.4828$; 12 months (EOS): $p = 0.1895$).

Change in restless leg syndrome score

The mean (SD) CH-RLSq score increased from 12.25 (4.57) at baseline to 13.50 (6.36) at 6 months and 14.50 (12.02) at 12 months (EOS) (higher values indicate a worsening of symptoms). However the increase was not statistical significant from baseline to 6 months ($p = 0.6392$) or 12 months (EOS) ($p = 0.7184$). Of the 8 subjects diagnosed with definite or probable RLS in the lead study, 4 subjects had definite or probable RLS symptoms at baseline in this study. Due to the low number of subjects in the analysis, the change in CH-RLS score should be interpreted with caution.

Change in disease activity status using Harvey-Bradshaw index for Crohn's disease or partial Mayo score for ulcerative colitis from baseline to month 6 and End of Study

There were no major changes in disease activity status using Harvey-Bradshaw index for Crohn's disease and partial Mayo score for ulcerative colitis from baseline to 6 months and 12 months (EOS).

Number of subjects who discontinued study

15 of 39 subjects discontinued the study. The reasons for pre-mature discontinuation included

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lost to follow-up, received investigational drug from another clinical study, withdrawal of consent, as per investigator's decision, or not able to attend scheduled visits. 2 subjects discontinued the study due to intolerance to iron isomaltoside 1000. Both subjects were administered iron sulphate in the lead-in study.

Change in platelet count from baseline to month 6 and end of study

There were no statistical significant changes in platelet count from baseline to 6 months (p = 0.5760) and 12 months (EOS) (p = 0.3020).

Summary of safety results

Overall, 57 AEs were reported by 26 (66.7 %) subjects during the study. Of these 57 AEs, 4 (perianal abscess, miliary tuberculosis, nephrolithiasis, and worsening of ulcerative colitis) were serious and 53 were non-serious AEs. All SAEs were not related to iron isomaltoside 1000 and the subjects recovered without sequelae except worsening of ulcerative colitis, which recovered with sequelae (bloody stools and increased bowel movement). Of 39 subjects, 17 (43.6 %) reported 28 mild AEs, 18 (46.2 %) reported 28 moderate AEs, and 1 (2.6 %) reported a severe AE (miliary tuberculosis) which was not related to the study drug and the subject recovered without sequelae. The majority (96.5 %) of the AEs were not related to the study drug. Of 39 subjects, 2 (5.1 %) reported 2 AEs (anaphylactoid reaction and hypersensitivity) which were probable related to iron isomaltoside 1000. In the case with reported term anaphylactoid reaction by investigator, [redacted] However, the subject developed flush, dyspnoea, and drop in oxygen saturation (without significant hypotension) after receiving 30 mg of iron isomaltoside 1000. In the case of reported term hypersensitivity by investigator, [redacted]. Both AEs were non-serious, moderate in severity and on follow-up the subjects recovered without sequelae. The study drug was immediately stopped in these 2 subjects and the subject experiencing anaphylactoid reaction as per reported investigator term was withdrawn from the study.

For the majority (73.7 %) of the AEs, the subjects recovered without sequelae, 12 AEs were on-going and follow-up was not necessary, and 3 AEs (multiple sclerosis, haemorrhoids, ulcerative colitis) recovered with sequelae. There were no deaths reported during this study.

Hypophosphatemia was not observed in any subjects. Clinical significant abnormalities were reported in the following laboratory parameters: CRP (3 subjects of which 2 reported elevated

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CRP levels compared to the previous visit), elevation of ALAT and ASAT (1 subject), and WBC (1 subject). The vital signs were comparable across visits for all subjects including those undergoing re-dosing. 13 abnormal observations in the physical examination were recorded in 8 subjects where 2 were clinically significant and 11 were clinically non-significant. The 2 clinically significant abnormal observations were palpable resistance epigastrium at baseline (1 subject) and toe and finger deformation at baseline, 6, and 12 months (EOS) (1 subject).

Conclusion

8/23 subjects with baseline Hb ≥ 12.0 g/dL and 3/12 subjects with baseline Hb < 12.0 g/dL were able to maintain Hb ≥ 12.0 g/dL at all follow-up visits.

The Kaplan-Meier estimate of time to a Hb < 12.0 g/dL estimated that 17 of the 23 subjects with a Hb ≥ 12.0 g/dL at baseline would maintain a Hb ≥ 12.0 g/dL up to 1 year with a probability of 0.638. This was in line with the crude LOCF estimate of 17/23 (74 %) of subjects able to maintain Hb ≥ 12.0 g/dL during the study.

The probability of maintaining a Hb ≥ 12.0 g/dL at 1 year in subjects with Hb < 12.0 g/dL at baseline was 0.313 which was predominantly due to subjects not achieving Hb ≥ 12.0 g/dL at the month 3 visit.

Two additional exploratory analyses were conducted on the primary endpoint. The first was to determine the maintenance of stable Hb ≥ 12.0 g/dL in subjects with baseline Hb ≥ 12 g/dL or reaching Hb ≥ 12.0 g/dL during the study and the second was to determine the maintenance of change in Hb ≥ 2.0 g/dL in subjects that had a response of Hb ≥ 2.0 g/dL at any visit in the lead-in study.75 % subjects with Hb ≥ 12 g/dL at baseline or any visit during the study were able to maintain a Hb ≥ 12.0 g/dL at any follow up visit and the Kaplan-Meier plot estimated that 24 subjects would maintain a Hb ≥ 12.0 g/dL at 1 year with a probability of 0.628. In this study, 48.6 % of the subjects that had a change in Hb ≥ 2.0 g/dL in the lead-in study had a probability of 0.707 of maintaining a change in Hb ≥ 2.0 g/dL at 1 year.

At every follow-up visit, a numerically higher proportion of subjects were able to maintain Hb ≥ 12.0 g/dL if their baseline Hb was ≥ 12.0 g/dL in comparison to subjects with baseline Hb < 12.0 g/dL.

34 subjects were re-dosed where 15 were dosed once, 10 were dosed twice, 3 were dosed thrice, and 6 subjects were dosed four times. Subjects with baseline Hb ≥ 12.0 g/dL were more frequently re-dosed once/twice and had a higher likelihood of maintaining a Hb ≥ 12.0 g/dL at 12 months. Re-dosing at a frequency of 3 or 4 times was observed more often in subjects with Hb < 12.0 g/dL and these subjects had less likelihood of maintaining Hb ≥ 12.0 g/dL.

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

Overall, the mean cumulative dose administered was 2192 mg (SD: 1580, range: 30:7000 mg) and the median single dose across visits was 1000 mg. 1000 mg of iron isomaltoside 1000 was administered to 11/27 subjects at baseline, 10/16 subjects at 3 months, 7/13 subjects at 6 months, and 4/12 subjects at 9 months while 12/27 subjects at baseline, 3/16 subjects at 3 months, 4/13 subjects at 6 months, and 4/12 subjects at 9 months received > 1000 mg of iron isomaltoside 1000. The mean single dose of iron isomaltoside 1000 re-administered at different visits was comparable (baseline: 1167 mg, 3 months: 1002 mg, 6 months: 1154 mg, 9 months: 1000 mg).

There was a statistical significant increase in *s*-iron, *s*-ferritin, and TSAT concentration and a non-significant decline in the TIBC concentration from baseline to 12 months (EOS). No statistical significant changes in total QoL, CH-RLSq score, and platelet counts were observed from baseline to 6 months and 12 months (EOS). There were no major changes in disease activity status for Crohn's disease and ulcerative colitis from baseline to 6 months and 12 months (EOS).

26 subjects reported 57 treatment emergent AEs where 4 AEs were SAEs (perianal abscess, miliary tuberculosis, nephrolithiasis, and worsening of ulcerative colitis). All SAEs were not related to iron isomaltoside 1000 and the subjects recovered without sequelae except worsening of ulcerative colitis, which recovered with sequelae (bloody stools and increased bowel movement). None of the AEs was fatal. Of 39 subjects, 2 subjects reported 2 AEs (investigators reporting term: anaphylactoid reaction and hypersensitivity, respectively) which were probable related to iron isomaltoside 1000. Both AEs were non-serious, moderate in severity, and on follow-up the subjects recovered without sequelae. The study drug was immediately stopped in these 2 subjects and the subject experiencing anaphylactoid reaction was withdrawn from the study.

None of the clinical significant abnormalities in laboratory parameters were reported as AEs. No abnormal, clinically significant ECG was reported at baseline or 12 months (EOS).

In conclusion, repetitive long term dosing was well tolerated in subjects with IBD and according to Kaplan-Meier plot able to maintain Hb ≥ 12.0 g/dL up to 1 year of study period in 17/23 IBD subjects with Hb ≥ 12.0 g/dL at baseline and in 4/12 of subjects with Hb < 12.0 g/dl at baseline.

Date of the report

20 January 2016