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Gybel-Brask, Mikkel; Seeberg, Jens; Thomsen, Lars L.; Johansson, Pär I.

Published in:
Transfusion

DOI (link to publication from Publisher):
10.1111/trf.14521

Publication date:
2018

Document Version
Publisher's PDF, also known as Version of record

Intravenous iron isomaltoside improves hemoglobin concentration and iron stores in female iron-deficient blood donors: a randomized double-blind placebo-controlled clinical trial

Mikkel Gybel-Brask,[1] Jens Seeberg,[1] Lars L. Thomsen,[2,3] and Pär I. Johansson[1]

BACKGROUND: This trial evaluated the efficacy and safety of intravenous (IV) iron isomaltoside (Monofer) in comparison with placebo in first-time female blood donors.

STUDY DESIGN AND METHODS: The trial was a prospective, double blind, placebo-controlled, randomized, comparative, single-center trial of 85 first-time female blood donors. The subjects were randomly assigned 1:1 to either 1000 mg IV iron isomaltoside infusion or placebo. The primary endpoint of the trial was change in hemoglobin (Hb) from baseline to right before the third blood donation.

RESULTS: The increase in Hb was significantly higher for iron isomaltoside compared with placebo right before both the second blood donation ($p = 0.0327$) and the third blood donation (primary endpoint, $p < 0.0001$). Improvements in other iron-related variables (plasma iron, plasma ferritin, transferrin saturation, and reticulocyte count) in favor of iron isomaltoside were also observed. The trial was not powered on patient-reported outcomes. However, improvements in iron stores and Hb levels after iron isomaltoside administration were supported by the fact that several of the fatigue symptoms scores showed numerical differences in favor of iron isomaltoside. There were no differences in side effects between the groups.

CONCLUSION: In iron-deficient female blood donors a single IV iron isomaltoside administration resulted in an improvement in Hb concentration and iron stores and demonstrated a favorable safety profile comparable to placebo.

Blood donors undergo a progressive decline in their iron reserves, which can lead to iron-deficient erythropoiesis. The prevalence of iron deficiency due to blood donation is significantly higher in menstruating women than in men and increases progressively as the frequency of donation increases.[1] According to a Danish trial, 31.7% of premenopausal female blood donors showed depleted iron reserves and 3.3% developed iron deficiency anemia.[2] In Denmark, female blood donors are deferred from blood donation if their hemoglobin (Hb) level is less than 12.5 g/dL[3] and it

ABBREVIATIONS: AE(s) = adverse event(s); FAS = full analysis set; p-ferritin = plasma ferritin; p-iron = plasma iron; PP = per protocol; RLS = restless leg syndrome; SAE(s) = serious adverse event(s); TEAE(s) = treatment-emergent adverse event(s); TSAT = transferrin saturation.

From the [1]Section for Transfusion Medicine, Department of Clinical Immunology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [2]Aalborg University, Aalborg, Denmark; and [3]Pharmacosmos A/S, Holbaek, Denmark.

Address reprint requests to: Pär I. Johansson, Section for Transfusion Medicine, Department of Clinical Immunology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; e-mail: Per.Johansson@regionh.dk.

The trial was funded by Pharmacosmos A/S (Holbaek, Denmark).

Received for publication November 1, 2017; revision received December 7, 2017; and accepted December 20, 2017.

doi:10.1111/trf.14521

TRANSFUSION 2018;58;974–981

is estimated that approximately 40% of all deferrals are due to low Hb levels and approximately 95% of those are women with childbearing potential.[4] This inevitably results in reduced donation frequency or cessation of donation if not managed with iron supplements.

In patients, treatment with oral iron is suboptimal because of limited absorption, lack of adherence, and intolerance—or insufficient when the iron need is high.[5,6] Therefore, intravenous (IV) iron is considered more effective and better tolerated and improves quality of life to a greater extent than oral iron in patients.[6-8] IV iron has not been evaluated in a healthy blood donor population.

Iron isomaltoside (Monofer, Pharmacosmos) is one of the newer IV iron formulations available. Clinical efficacy and safety data are available for iron isomaltoside administered to different patients groups with or without anemia.[9-16] However, there is a need for clinical efficacy and safety data within healthy women with iron deficiency without anemia, which is, for example, observed in blood donors.

MATERIALS AND METHODS

Trial design

This prospective, double-blind, placebo-controlled, randomized, comparative, single-center trial was conducted in Denmark from June 2013 to December 2016 in female first-time blood donors at the Section for Transfusion Medicine, Department of Clinical Immunology, Rigshospitalet, Copenhagen University Hospital. The objectives of this trial were to evaluate the efficacy and safety of IV iron isomaltoside in comparison with placebo in first-time female blood donors. The subjects attended four to five visits: first blood donation (Visit 0), screening visit (Visit 1), baseline or treatment visit (Day 0; Visit 2), voluntary exercise visit (Week 3; Visit 2a), second blood donation (12 weeks from first blood donation; Visit 3), and third blood donation (12 weeks from second blood donation; Visit 4) during the 24-week trial period. All assessments performed at each trial visit are shown in Table S1 (available as supporting information in the online version of this paper).

The trial protocol and other related documents were approved by competent authorities and the local ethics committee (The Committees on Health Research Ethics for the Capital Region of Denmark, approval date June 13, 2012; Approval H-3-2012-039). The trial was conducted in accordance with good clinical practice and the Declaration of Helsinki. Informed consent was obtained in writing before any trial-related activities. The trial is registered at ClinicalTrials.gov (Identifier NCT01895231).

Participants

Women at least 18 years of age, who were first-time donors and had a plasma ferritin (p-ferritin) concentration of less than 60 ng/mL were considered eligible to participate in the trial. Hb concentration was routinely measured in all donors using an EDTA-anticoagulated predonation venous sample analyzed on a hematology analyzer (Sysmex XE-2100D, Sysmex Corp.). P-ferritin was routinely measured in all first-time donors using a predonation serum sample on an immunodiagnostic system (Vitros 3600 or Vitros 5600, Ortho Clinical Diagnostics). Eligible donors were approached by telephone within 2 weeks of their first blood donation. Donors willing to participate were included after having signed the informed consent form. The exclusion criteria were iron overload or disturbances in utilization of iron (e.g., hemochromatosis and hemosiderosis); known hypersensitivity to any excipients in the investigational drug products; history of drug-related allergies or severe asthma; decompensated liver cirrhosis and hepatitis (defined as alanine aminotransferase > 3 times upper limit of normal); active acute or chronic infections (assessed by clinical judgment supplied with white blood cell counts and C-reactive protein); rheumatoid arthritis with symptoms or signs of active inflammation; women who were pregnant or nursing; participation in any other clinical trial where the trial drug had not passed five half-lives before the screening; untreated vitamin B_{12} or folate deficiency; treatment with other IV or oral iron products, including iron-containing multivitamins within 4 weeks before the screening; treatment with erythropoietin within 4 weeks before the screening; and any other medical condition that, in the opinion of the investigator, might cause the subject to be unsuitable for the completion of the trial or place the subject at potential risk from being in the trial. During the trial commencement, inclusion criterion "p-ferritin < 30 μg/L" was changed to "p-ferritin < 60 μg/L" since fewer women than expected had a p-ferritin level of less than 30 μg/L and a p-ferritin level of less than 60 μg/L was also the normal criterion at the site for initiating iron treatment. Furthermore, specific list of contraceptives required was changed to a more general term "adequate contraception (e.g., intrauterine devices, hormonal contraceptives, or double-barrier method)." Thus, women using the double-barrier method or who were sexually inactive could also be included.

Any concomitant medication or treatment deemed necessary to provide adequate supportive care was allowed throughout the trial except the erythropoiesis-stimulating agent treatment and any iron supplementation other than investigational drug including iron-containing multivitamins as this would influence the outcome measures of the trial. During the trial, Hb concentration, complete hematology set, p-ferritin, p-vitamin B12, serum folate, transferrin saturation (TSAT), plasma iron (p-iron), serum phosphate, and routine biochemistry were measured as routine clinical samples at one laboratory at the Department of Clinical Biochemistry, Rigshospitalet.

Randomization and interventions

The enrolled subjects were randomly assigned 1:1 to receive either iron isomaltoside or placebo (sodium

chloride; Natriumklorid 9 mg/mL, Fresenius Kabi). Subjects in the iron isomaltoside group (43 subjects) received a single-IV-dose infusion of 1000 mg of iron isomaltoside over at least 15 minutes. Subjects in the placebo group (42 subjects) received saline as a single-dose infusion of 100 mL over at least 15 minutes.

Permuted block randomization with a block size of 6 was used to randomize the subjects. The randomization list was prepared centrally by a contract research organization, Max Neeman International Data Management Center, using a validated computer program (Statistical Analysis Software [SAS] 9.1.3, SAS Institute, Inc.) PROC PLAN procedure. An interactive Web response system method was used to randomize the eligible subjects to the treatment groups. When the subject data had been entered into the interactive Web response system, a unique randomization number was generated for the subject, identifying which treatment the subject was allocated to. The screening and enrollment of the subjects were performed by the investigator at the site, whereas the entering of the subject data into the interactive Web response system generating the randomization number was performed by the trial nurse or trial coordinator.

Blinding

The trial was double-blinded and thus both the subjects and the investigators were blinded. Randomization, preparation, and connection of infusions were handled by personnel otherwise unrelated to the trial. To ensure that, the infusion bags and all visible disposables were wrapped in aluminum foil by the personnel unrelated to the trial. All used material was removed by the same person without revealing the infused fluid.

Objectives and endpoints

The primary objective of the trial was to evaluate the effect of IV iron isomaltoside compared with placebo on Hb. The secondary objectives were to evaluate the effect of iron isomaltoside compared with placebo on tolerance of three blood donations, other relevant iron-related biochemical variables, fatigue, restless leg syndrome (RLS) symptoms, exercise tolerance, and safety.

The primary endpoint was to compare the change in Hb concentration from baseline to right before the third blood donation in the two trial arms. The secondary efficacy endpoints were to measure and compare the following in the two trial arms: change in Hb concentrations from baseline to right before second donation; number of subjects who could not tolerate three donations due to Hb concentration below the limit of acceptance (12.5 g/dL in women); change in concentrations of p-iron, p-ferritin, TSAT, and reticulocyte count from baseline to 12 weeks after first and second blood donations; change in fatigue symptoms from baseline to 12 weeks after first and second blood donations measured by the Fatigue Visual Numeric Scale and five questions from the Fatigue Severity Scale; change in RLS symptoms from baseline to 12 weeks after first and second blood donations measured by the Cambridge-Hopkins Restless Legs Syndrome questionnaire; change in exercise tolerance from baseline to 3 weeks after baseline measured by a two-step test on a bike; and safety (adverse events [AEs], vital signs, electrocardiogram, serum phosphate, and hematology and biochemistry variables). All efficacy outcomes were tested for superiority whereas safety outcomes were summarized descriptively.

Sample size

The sample size calculation used the following assumptions: superiority analysis, normally distributed data, Type 1 error of 5%, two-sided test, and power of 80%. The null hypothesis was that no effect was present. With a sample size of 37 subjects per treatment group and an assumed standard deviation (SD) in Hb level of 1.5 g/dL, the trial was able to detect a difference of 1.0 g/dL in change in Hb concentration from baseline to right before the third blood donation.

Statistical analysis

The following data sets were used in the analysis (Fig. 1):

- Safety analysis set (n = 82): The safety analysis set included all the subjects who were randomly assigned and received at least one dose of investigational product.
- Full analysis set (FAS; n = 80): The FAS included all the subjects who were randomized into the trial, received at least one dose of investigational product, and had at least one postbaseline Hb assessment.
- Per protocol (PP; n = 74): The PP population included all the subjects in the FAS who did not have any major protocol deviations.

The primary analyses were conducted on the FAS and PP analysis set. The secondary analyses were conducted on the FAS, and the safety analyses were conducted on the safety population.

The primary efficacy analysis and all secondary efficacy endpoints related to "change from baseline" were performed using an analysis of covariance with treatment as factor and baseline value as covariate. The number of subjects who could not tolerate three blood donations was compared between iron isomaltoside and placebo treatment groups using a chi-square or Fisher's Exact test.

Adverse events were coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1. All the safety data were summarized descriptively.

All statistical analyses were performed using computer software (SAS, Version 9.4, SAS Institute). All statistical tests were carried out as two-sided on a 5% level of significance and all confidence intervals (CIs) were 95% intervals.

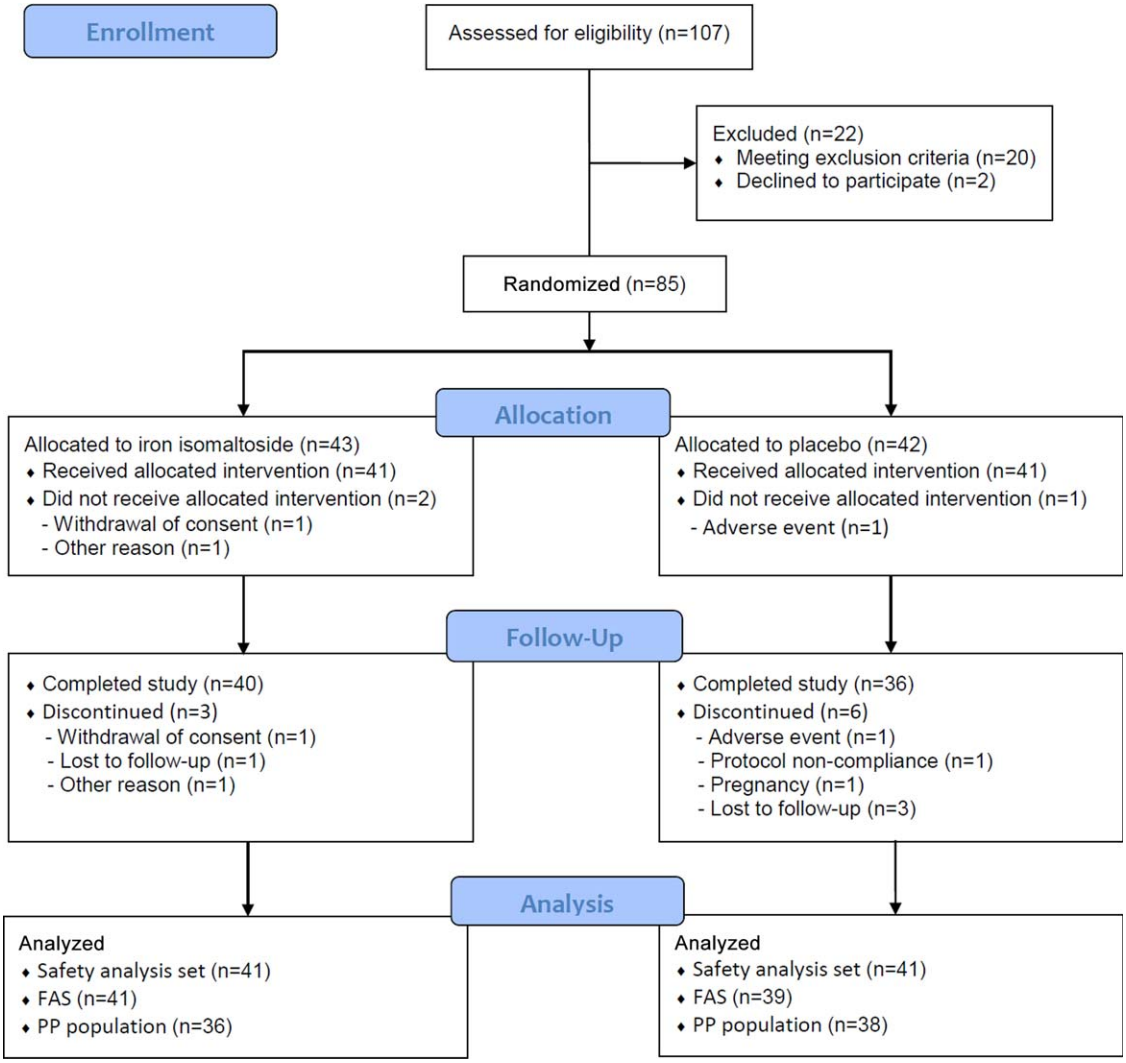

Fig. 1. Subject disposition.

RESULTS

Subjects

A total of 107 subjects were screened from June 2013 to June 2016 and 85 of these were randomized into the trial (43 subjects in the iron isomaltoside group and 42 subjects in the placebo group). Overall, discontinuation was slightly higher in the placebo group (iron isomaltoside group, 7.0% [3/43]; placebo group, 14.3% [6/42]). Details of subject disposition are summarized in Fig. 1. Subject demographics and baseline characteristics are summarized in Table 1.

Exposure to iron

All 41 subjects exposed to iron isomaltoside received the full dose of 1000 mg. Of the 41 subjects receiving placebo, two subjects received slightly less than the planned infusion volume (94 and 85%, respectively) due to technical problems.

Efficacy results

Changes in Hb concentration

The primary endpoint of the trial was change in Hb concentration from baseline to right before the third blood donation (Visit 4). The analysis was conducted on the FAS (n = 80) and PP (n = 74) analysis set. The difference estimate between the two treatments groups was 1.25 (95% CI, 0.90-1.61; $p < 0.0001$) in favor of iron isomaltoside in the FAS ($p < 0.0001$; Fig. 2, Table 2), and similar results were shown in the PP analyses ($p < 0.0001$; Table 2).

Statistical analysis of the secondary endpoint, change in Hb concentration from baseline to right before the second blood donation (Visit 3) on the FAS (n = 78), is presented in Table 2. The increase in Hb concentration was significantly greater for iron isomaltoside compared with placebo (difference estimate, 0.35; 95% CI, 0.03-0.68; $p = 0.0327$). The number of subjects who could not tolerate three blood donations due to Hb concentration below the

TABLE 1. Subject demographics and baseline characteristics

Statistics/category	Treatment group: Iron isomaltoside (n = 43)	Placebo (n = 42)
Age (years)		
Mean (±SD)	23.2 (3.75)	24.9 (6.01)
Median	23.0	23.0
Range	18-35	18-45
Ethnic origin, n (%)		
Caucasian	43 (100.0)	41 (97.6)
Asian		1 (2.4)
Current smoker, n (%)		
Yes	6 (14.0)	15 (35.7)
No	37 (86.0)	27 (64.3)
Weight (kg)		
Mean (±SD)	63.2 (8.4)	64.2 (9.2)
Median	62.0	62.7
Range	51.2-89.4	52.0-92.0
Biochemistry at baseline, mean (±SD)		
Hb (g/dL)	12.3 (0.6)	12.4 (0.8)
TSAT (%)	15.2 (8.3)	14.1 (7.2)
Ferritin (ng/mL)	16.4 (6.5)	14.0 (6.1)

limit of acceptance of 12.5 g/dL did not differ significantly between iron isomaltoside and placebo (14/41 [34.1%] vs. 16/39 [41.0%] of subjects; p = 0.5252).

Changes in iron indices

There was a mean increase in p-iron, p-ferritin, and TSAT in the iron isomaltoside group from baseline to right before the second blood donation (Visit 3). There was also an increase in p-iron and TSAT in the placebo group, whereas p-ferritin remained essentially unchanged. The observed increase was significantly higher in the iron isomaltoside group (p-iron, p = 0.0310; p-ferritin, p < 0.0001; TSAT, p = 0.0002; Table S2 [available as supporting information in the online version of this paper]; Fig. 2). Mean reticulocyte count decreased from baseline to right before the second blood donation (Visit 3) in both treatment groups, but the decrease was statistically significantly less in the iron isomaltoside group (p = 0.0219; Table S2, Fig. 2). At the third blood donation (Visit 4), the change from baseline observed for p-iron, p-ferritin, and TSAT was significantly higher in the iron isomaltoside group (p-iron, p = 0.0002; p-ferritin, p < 0.0001; TSAT, p < 0.0001; Table S2, Fig. 2).

Donor fatigue and exercise tolerance

Overall, the mean fatigue symptoms scores appeared to decrease from baseline during the trial for both treatment groups (by up to 27%). The only exception was the Fatigue Severity Scale question "Fatigue interferes with my work, family, or social life," where the score decreased during the trial in the iron isomaltoside group (1.93, 1.78, and 1.82 at baseline, Visit 3, and Visit 4, respectively) but increased in the placebo group (2.38, 2.69, and 2.29 at baseline, Visit 3, and Visit 4, respectively; p = 0.0164). For the Fatigue Visual Numeric Scale score, the decrease from baseline to right before the second blood donation (Visit 3) tended to be greater for iron isomaltoside than for placebo (p = 0.0747). Otherwise, no significant treatment differences were seen with respect to change in fatigue symptoms scores (Table S3, available as supporting information in the online version of this paper).

Only very few subjects reported probable or definite presence of RLS in both treatment groups (two subjects for iron isomaltoside and three subjects for placebo). There were no relevant changes during the trial in the number of subjects reporting probable or definite presence of RLS (data not shown).

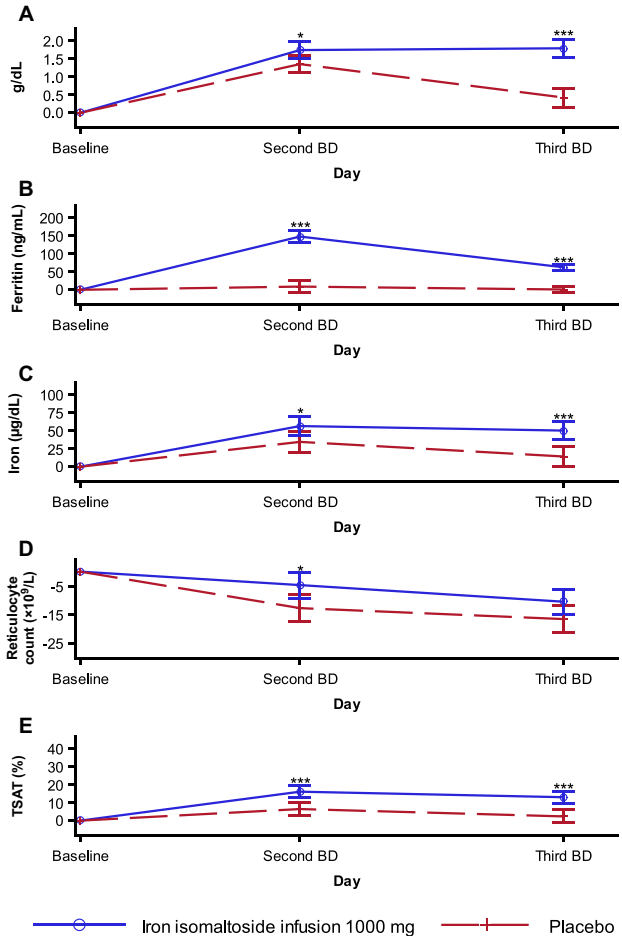

Fig. 2. Changes in Hb, p-iron, p-ferritin, TSAT, and reticulocyte count from baseline to right before the second and third blood donations (mean ± SE), FAS. Estimates (mean and 95% CI) from a mixed model with repeated measures with treatment and time as factors, treat × time interaction, and baseline value as covariate. *p < 0.05, **p = 0.001 to 0.01, ***p < 0.001. BD = blood donation.

TABLE 2. Analysis of change in Hb concentration (g/dL) from baseline to right before the second and third blood donations

Endpoint, analysis set (number of subjects)	Iron isomaltoside (Group A), LS mean	Placebo (Group B), LS mean	Difference estimates (95% CI)	p value
FAS				
Second blood donation (Group A, 40; Group B, 38)	1.7116	1.3578	0.3538 (0.0300-0.6780)	0.0327
Third blood donation (Group A, 41; Group B, 39)	1.7912	0.5385	1.2527 (0.8979-1.6076)	<0.0001
PP				
Third blood donation (Group A, 36; Group B, 38)	1.8506	0.5452	1.3054 (0.9357-1.6751)	<0.0001

LS mean = least square mean.

A total of 26 subjects treated with iron isomaltoside and 28 receiving placebo performed an exercise tolerance test. The workload and heart rate at the two steps of the incremental bicycle exercise test appeared similar for the two treatment groups and no significant treatment differences were observed (data not shown).

Safety

In the iron isomaltoside group, 54 treatment-emergent AEs (TEAEs) were reported in 28 subjects (68.3% of subjects), while in the placebo group, 78 TEAEs were reported in 31 subjects (75.6% of subjects). The most frequently reported TEAEs were nasopharyngitis (17.1 and 17.1% of subjects in the iron isomaltoside and placebo groups, respectively), headache (4.9 and 9.8%), dizziness (4.9 and 9.8%), and anemia (0.0 and 12.2%). Except for anemia, which was only reported in the placebo group, no other specific patterns were identified when comparing TEAEs between iron isomaltoside and placebo groups.

The TEAEs were mild (78% in the iron isomaltoside group and 73% in the placebo group) or moderate (22% in the iron isomaltoside group and 27% in the placebo group). No severe TEAEs were reported. The majority of TEAEs were recovered/resolved or recovering/resolving at the end of trial (85% in the iron isomaltoside group and 81% in the placebo group).

A total of three treatment-emergent serious AEs (SAEs) occurred during the trial (two SAEs in two subjects in the iron isomaltoside group and one SAE in the placebo group). The two SAEs in the iron isomaltoside group were one spontaneous abortion and one pregnancy, and the SAE in the placebo group was a spontaneous abortion. All three SAEs were moderate in severity and assessed by the investigator not to be related to investigational product.

In the iron isomaltoside group, four TEAEs in four subjects were assessed to be possibly related or related to investigational product (influenza-like illness, infusion site irritation, cystitis, and urticaria), while in the placebo group, seven TEAEs in five subjects were assessed to be possibly related to investigational product (dyspepsia, vomiting, pain, arthralgia, headache, RLS, and hypotension).

There was one subject (2%) in the iron isomaltoside group with p-phosphate levels of less than 2 mg/dL at any time. The subject had a p-phosphate level of 1.92 mg/dL at the third blood donation. The event was assessed as nonclinically significant and not reported as an AE. No relevant changes were seen in any of the safety-related hematology or biochemistry variables during the trial.

There were no mean differences in systolic or diastolic blood pressure or in heart rate between iron isomaltoside and placebo. All electrocardiograms were assessed to be normal, and there were no abnormal clinically significant findings in the physical examinations or safety issues observed with safety laboratory variables.

DISCUSSION

The prevalence of iron deficiency among blood donors is high.[17] Iron deficiency may lead to an increased prevalence of fatigue; decreased physical endurance; and impairments in attention, concentration, and other cognitive functions,[18-20] which reduces donation frequency and in worst cases ceases donation. According to data from the REDS-II donor centers, approximately 10% of all donation attempts (17.7% women; 1.6% men) end in a deferral due to a low Hb or hematocrit.[17] The blood donors need to be managed with iron supplements to keep up with the blood losses, and by maintaining healthy iron levels donors will be able to safely continue donating thereby ensuring a robust blood supply.

In the Hemoglobin and Iron Recovery Study (HEIRS), a randomized nonblinded clinical trial, low-dose iron supplementation (37.5 mg of elemental iron daily) or no iron was given for 24 weeks. Recovery of iron stores in all participants who received iron supplements took a median of 76 days and for participants not taking iron, median recovery time was longer than 168 days ($p < 0.001$). Without iron supplements, 67% of participants did not recover iron stores by 168 days.[21]

However, it can be difficult to ensure adherence to oral iron supplementation because of the gastrointestinal side effects such as constipation. Furthermore, the absorption of oral iron is limited, and therefore oral iron is

not the optimal treatment when the iron need is high. Instead IV iron may be a more efficient and convenient treatment of blood donors, and this randomized, prospective, double-blind, parallel, comparative placebo-controlled, single-center trial was planned to evaluate the efficacy and safety of IV iron isomaltoside in comparison with placebo in first-time female blood donors. Improvements in both Hb and other iron-related biochemical variables (p-iron, p-ferritin, TSAT, and reticulocyte count) were observed in the iron isomaltoside group compared with placebo. The increase in Hb observed before the second blood donation in the placebo group is most likely a physiologic compensation of the blood loss. However, between the second and third blood donations, Hb decreases in the placebo group indicating that the iron stores are depleted.

The improvements in Hb and iron stores did not lead to greater completion rate of blood donations. Even though the number of subjects who could not tolerate three blood donations due to Hb concentration below the limit of acceptance of 12.5 g/dL was numerically lower in the iron isomaltoside group, the trial was not powered to this endpoint and it did not reach significance.

The trial was not powered to patient-reported outcomes. However, the improvements in iron stores and Hb levels after IV iron isomaltoside administration compared with placebo was supported by the fact that several of the fatigue symptoms scores showed numerical differences in favor of iron isomaltoside and the fatigue score for "Fatigue interferes with my work, family, or social life" decreased significantly in the iron isomaltoside group. No significant differences were observed in RLS symptoms or exercise tolerance.

Intravenous iron isomaltoside administration was well tolerated with a safety profile similar to placebo. Three SAEs occurred, which were all assessed by the investigator not to be related to investigational product. There was a numeric higher frequency of related TEAEs in the placebo group supporting the fact that there were no safety issues with iron isomaltoside. This trial also indicates that hypophosphatemia with IV iron isomaltoside treatment appears not to be a concern.

The use of IV medication in healthy donors could be of ethical concern and donor preferences are unknown—it is believed that many donors stop taking oral iron supplementation due to unpleasant gastrointestinal side effects, and these side effects would be eliminated with IV iron. Although we believe that IV iron administration is feasible in our blood donation facility, this might not be the case everywhere. The price of IV iron isomaltoside is somewhat higher than a course of oral iron supplementation, which should be weighed against the efficacy; this should be investigated further.

We believe that the internal validity of the trial is high, owing to the prospective double-blind, randomized, and placebo-controlled design. Whether the results are generalizable to the entire donor population is uncertain, as we included only female, first-time donors. Further trials including returning donors and male donors on a larger scale are warranted. In conclusion, a single IV iron isomaltoside administration resulted in an improvement in Hb concentration and iron stores and demonstrated a favorable safety profile comparable to placebo.

ACKNOWLEDGMENTS

The authors acknowledge the investigators and trial personal for their contribution to the trial, the statistical support from Jens-Kristian Slott Jensen and Slott Stat, and the medical writing assistance of Eva-Maria Damsgaard Nielsen in editing the manuscript. Eva-Maria Damsgaard Nielsen is employed by Pharmacosmos A/S.

CONFLICT OF INTEREST

LLT is employed by Pharmacosmos A/S, and the institution (Section for Transfusion Medicine, Department of Clinical Immunology, Rigshospitalet, Copenhagen University Hospital, Denmark) received a fee per subject. After the trial was finalized, JS was employed by Pharmacosmos A/S. MGB and PIJ have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1. Trial flowchart
Table S2. Changes in p-iron, p-ferritin, TSAT, and reticulocyte count from baseline to right before the second and third blood donation, full analysis set
Table S3. Analysis of change from baseline in fatigue symptoms scores, full analysis set