A randomized, open-label trial of iron isomaltoside 1000 (Monofer®) compared with iron sucrose (Venofer®) as maintenance therapy in haemodialysis patients

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ABSTRACT

Background. Iron deficiency anaemia is common in patients with chronic kidney disease, and intravenous iron is the preferred treatment for those on haemodialysis. The aim of this trial was to compare the efficacy and safety of iron isomaltoside 1000 (Monofer®) with iron sucrose (Venofer®) in haemodialysis patients.

Methods. This was an open-label, randomized, multicentre, non-inferiority trial conducted in 351 haemodialysis subjects randomized 2 : 1 to either iron isomaltoside 1000 (Group A) or iron sucrose (Group B). Subjects in Group A were equally divided into A1 (500 mg single bolus injection) and A2 (500 mg split dose). Group B were also treated with 500 mg split dose. The primary end point was the proportion of subjects with haemoglobin (Hb) in the target range 9.5–12.5 g/dL at 6 weeks. Secondary outcome measures included haematology parameters and safety parameters.

Results. A total of 351 subjects were enrolled. Both treatments showed similar efficacy with >82% of subjects with Hb in the target range (non-inferiority, P = 0.01). Similar results were found when comparing subgroups A1 and A2 with Group B. No statistical significant change in Hb concentration was found between any of the groups. There was a significant increase in ferritin from baseline to Weeks 1, 2 and 4 in Group A compared with Group B (Weeks 1 and 2: P < 0.001; Week 4: P = 0.002). There was a significant higher increase in reticulocyte count in Group A compared with Group B at Week 1 (P < 0.001). The frequency, type and severity of adverse events were similar.

Conclusions. Iron isomaltoside 1000 and iron sucrose have comparative efficacy in maintaining Hb concentrations in haemodialysis subjects and both preparations were well tolerated with a similar short-term safety profile.

Keywords: chronic kidney disease, iron isomaltoside 1000, iron treatment

INTRODUCTION

Patients on haemodialysis frequently suffer from anaemia due to relative reduced renal erythropoietin production, as well as absolute and functional iron deficiency [1–3]. The latter can be optimally managed by intravenous (IV) iron repletion, which is superior to oral iron in this patient population [4–8].

It is estimated that a patient on haemodialysis loses 2–3 g of iron per year [9]. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend a trial of IV iron administration to patients on haemodialysis, [4] since maintenance of stable haemoglobin (Hb) and iron stores remains challenging due to continuous blood loss and increased iron utilization in this patient population. The KDIGO guidelines recommend that when prescribing iron therapy, one must first balance the potential benefits of avoiding or minimizing blood transfusions, erythropoiesis stimulating agent (ESA) therapy and anaemia-related symptoms against the risks of harm in individual patients of use of IV iron. In adult chronic kidney disease (CKD) patients with anaemia and who are not on iron or ESA therapy, the guideline suggests a trial of IV iron

if an increase in Hb concentration without starting ESA treatment is desired and the transferrin saturation (TSAT) is <30% and ferritin is <500 ng/mL. For adult CKD patients on ESA therapy who are not receiving iron supplementation, the guideline suggests a trial of IV iron if an increase in Hb concentration or a decrease in ESA dose is desired and the TSAT is <30% and ferritin is <500 ng/mL. Subsequent iron administration in CKD patients is based on Hb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA-treated patients, trends in each parameter and the patient's clinical status.

Iron sucrose (Venofer®) is currently one of the most widely used IV iron in haemodialysis patients with long-established efficacy and short-term safety [10, 11]. Compared with more recently introduced IV iron products, the iron is more loosely bound in iron sucrose [12]. This is associated with catalytic/labile iron which has been hypothesized to cause increased oxidative stress with potential consequences on long-term toxicity [13, 14]. The potential clinical risk in relation to e.g. increased risk of infection and cardiovascular morbidity is not known.

Iron complexes with more tightly bound iron such as iron isomaltoside 1000 (Monofer®) may offer a lower risk of labile iron toxicity from its binding to the carbohydrate moiety and hence a possibility of larger dose per administration [12]. The fact that a larger dose may be administered may be an advantage since according to the European Medicine Agency (EMA) there is a risk of an allergic reaction with every dose of IV iron that is given [15]. Currently, the larger single dose possibility has not been directly compared with more frequent lower dosing.

The aim of this head-to-head comparative trial was to explore the efficacy and short-term safety of iron isomaltoside 1000 administered as a single bolus or split bolus injection compared with iron sucrose in haemodialysis patients. The primary objective was to demonstrate that iron isomaltoside 1000 is non-inferior to iron sucrose in maintaining Hb levels between 9.5 and 12.5 g/dL. The secondary objectives were to assess other relevant haematology parameters, the effect on quality of life (QoL) and safety.

MATERIALS AND METHODS

Trial design

This prospective, randomized, comparative, open-label, non-inferiority, multi-centre trial was conducted from June 2011 to October 2013. The protocol and amendments were approved by local ethics committees/Institutional Review Boards and competent authorities (EudraCT number: 2010-023471-26). The trial was conducted in accordance with good clinical practice and the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (NCT01222884) 15 October 2010. Informed consent was obtained in writing prior to any trial-related activities.

Participants

The trial took place at 48 sites (hospitals or private dialysis clinics); 16 centres in India, 14 centres in the UK, 4 in Russia, 4 in Poland, 3 in Sweden, 3 in Switzerland, 2 in Romania, 1 in Denmark and 1 in the USA. Subjects ≥18 years of age with a diagnosis of CKD and on haemodialysis therapy for at least 90 days, Hb concentration between 9.5 and 12.5 g/dL (inclusive both values) both at screening visit 1a and screening visit 1b (screening visits were separated by at least 1 week), serum-ferritin <800 ng/mL, TSAT < 35% and receiving ESA treatment with stable dose for the previous 4 weeks prior to screening were enrolled. The complete inclusion and exclusion criteria are summarized in Table 1.

Interventions

All subjects received a cumulative dose of 500 mg iron.

Subjects in subgroup A1 were administered iron isomaltoside 1000 as a single undiluted IV bolus injection of 500 mg over ~2 min at baseline, subjects in subgroup A2 were administered undiluted iron isomaltoside 1000 in split doses of 100 mg at baseline and 200 mg each at Weeks 2 and 4 as IV bolus injections over ~2 min. Subjects in Group B were administered undiluted iron sucrose in split doses of 100 mg at baseline and 200 mg each at Weeks 2 and 4. The doses of iron sucrose were administered as per local summary product of characteristics or package insert and/or local hospital guidelines, as applicable.

All dosages were administered during dialysis, at least 30 min after the start and at least 1 h before the end of dialysis.

During the trial, the subjects were prohibited from having a blood transfusion and any iron supplementation other than investigational product starting from visit 1a.

Treatment with ESA had to be kept stable during the trial. The patients received different dosing schedules with various ESAs including epoetin alfa, epoetin beta, darbepoetin alfa, erythropoietin and methoxy polyethylene glycol-epoetin beta.

Objective and outcomes

The subjects attended six visits: screening visit (visit 1 was divided into visit 1a and visit 1b; visit 1a was held within 16 days before the baseline visit), baseline (visit 2), three on-treatment and follow-up visits (visits 3–5) and one end-of-trial visit (visit 6) during an 8-week period.

The trial was designed with the primary objective to demonstrate non-inferiority.

The primary efficacy outcome was to determine the proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (inclusive both values) at Week 6. The secondary efficacy outcome included assessment of the change in Hb concentration from baseline to Weeks 2, 4 and 6, change in concentrations of serum-iron, TSAT, serum-ferritin and reticulocyte count from baseline to Weeks 1, 2, 4 and 6, and change in total QoL score (Linear Analogue Scale Assessment) from baseline to Weeks 4 and 6. The safety outcomes of the trial were to determine the number of subjects who experienced any adverse drug reaction (ADR), including any suspected unexpected serious adverse reaction and safety laboratory assessments. The primary outcome was tested for non-inferiority whereas the remaining outcomes were tested for superiority.

Table 1. Inclusion and exclusion criteria

Inclusion criteria:
- Subjects ≥18 years of age with a diagnosis of CKD and on haemodialysis therapy for at least 90 days
- Hb concentration between 9.5 and 12.5 g/dL (inclusive both values) both at screening visit 1a and screening visit 1b (screening visits were separated by at least 1 week)
- Serum-ferritin <800 ng/mL, TSAT <35%
- Erythropoiesis stimulating agent treatment with dose stable for the previous 4 weeks prior to screening
- No IV iron or an average of no >100 mg/week for the previous 4 weeks
- Life expectancy beyond 12 months
- Willing to provide written informed consent

Exclusion criteria:
- Factors other than renal-related anaemia
- Iron overload or disturbances in utilization of iron (i.e. haemochromatosis and hemosiderosis)
- Currently undergoing active treatment with immunosuppressive agents
- Difference of Hb ≥1.0 g/dL between screening visit 1a and 1b
- A history of multiple allergies
- Decompensated liver cirrhosis or active hepatitis
- History of hepatitis B or C
- Active acute or chronic infections
- Rheumatoid arthritis with symptoms or signs of active joint inflammation
- Pregnant or nursing women
- Blood transfusion within the previous 12 weeks
- Planned elective surgery in the next 8 weeks
- Participation in any other clinical trial where the trial drug had not passed five half-lives prior to screening
- Untreated vitamin B_{12} or folate deficiency
- Any other medical condition that, in the opinion of the investigator, may have caused the patient to be unsuitable for completion of the trial or placed the patient at potential risk from being in the trial

Sample size and randomization

A stratified block randomization methodology was used in the trial to assign subjects in a 1 : 1 : 1 ratio (2 : 1 randomization to Groups A and B) to receive either iron isomaltoside 1000 as a single dose (Group A1), iron isomaltoside 1000 as a split dose (Group A2) or iron sucrose (Group B). The block size was six. The randomization list was prepared by a Contract Research Organization, Max Neeman International Data Management Centre, using a validated computer program (SAS 9.1.3, SAS Institute Inc., Cary, NC, USA) PROC PLAN procedure. An interactive web response system (IWRS) was used to randomize the subjects to the treatment groups. When the patient data had been entered into the IWRS, a unique randomization number was generated, which identified the treatment the patient was allocated to. The randomization of patient was stratified by serum-ferritin (<100 versus ≥100 ng/mL).

The trial was not blinded, however, since the primary outcome was a biochemical measurement it is unlikely to be affected by the open-label trial design.

With a 2 : 1 randomization, a two-sided significance level of 0.05, and a non-inferiority margin of 10% point, there was 80% power to demonstrate non-inferiority with 214 subjects in Group A and 107 subjects in Group B. Less than 10% of drop-outs were expected. As the trial was designed to demonstrate non-inferiority, the analyses of the full analysis set (FAS) and the per protocol (PP) population should lead to similar conclusions and therefore the analyses for both analyses sets needed to be powered properly. With ∼10% (anticipated) of subjects having major protocol violations, a total of 351 subjects were to be randomized (234 to iron isomaltoside 1000 and 117 to iron sucrose).
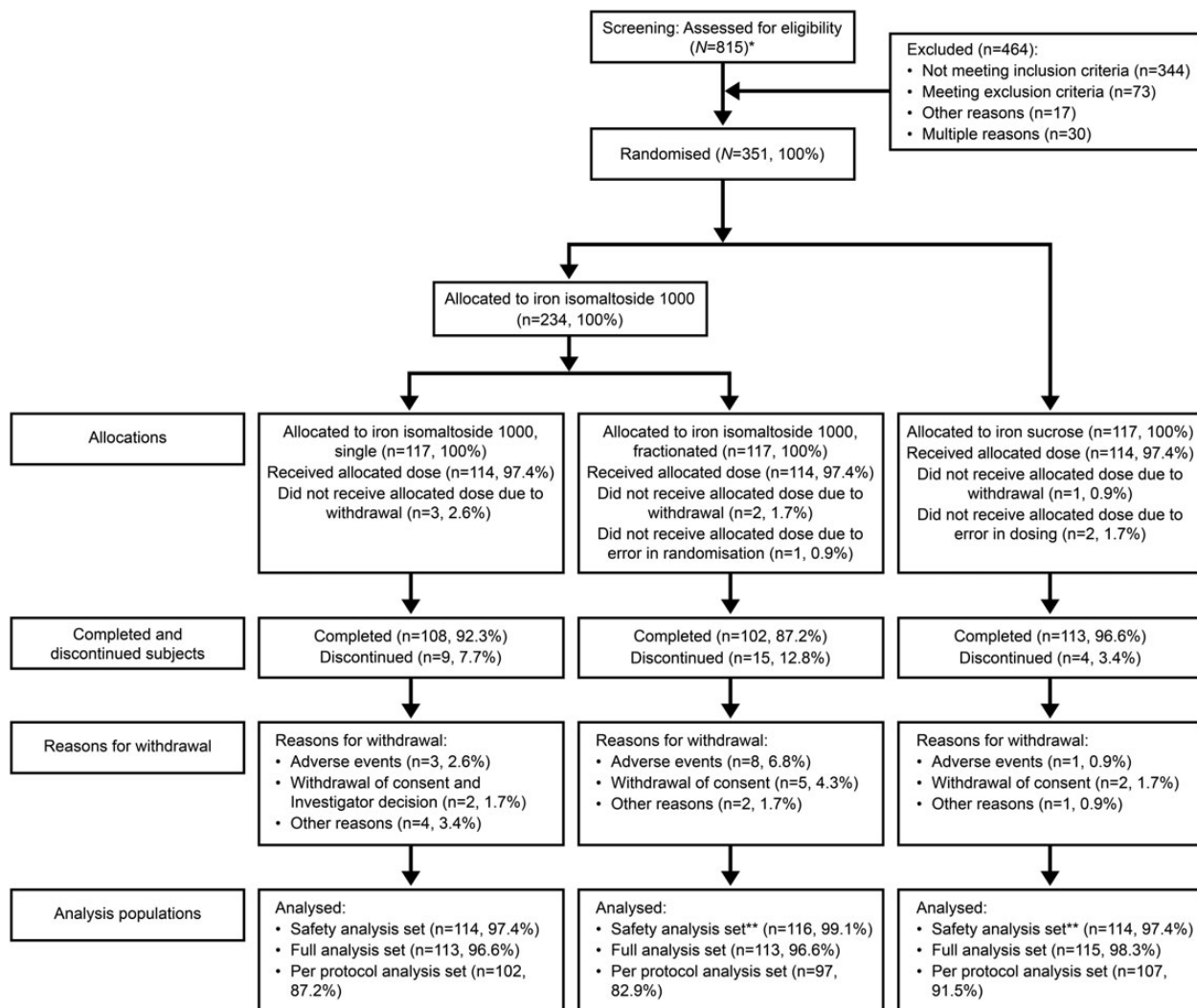
Statistical methods

The following data sets were used in the analyses (Figure 1).

The randomized population ($N = 351$) included all subjects who were randomized in the trial. The safety population ($N = 344$) included all subjects who were randomized and received at least one dose of the trial drug. The FAS population ($N = 341$) included all subjects who were randomized into the trial, received at least one dose of the trial drug, and had at least one post-baseline Hb assessment. The PP population ($N = 306$) included all subjects in the FAS who did not have any major protocol deviation of clinical or statistical relevance.

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

The primary outcome was summarized using number and percentage of subjects. A generalized linear model using the identity link function was used to compare the proportion of subjects with Hb concentration between 9.5 and 12.5 g/dL (both values included) at Week 6 using the last observation

FIGURE 1: Patient disposition.

*A total of 815 screenings were performed in 660 subjects. **Two subjects, who were allocated to treatment with iron sucrose, received fractionated iron isomaltoside 1000. These two subjects were included in the safety population in the iron isomaltoside 1000, fractionated subgroup.

Patients who were not dosed were excluded from the safety analysis set, patients who did not have a post-baseline haemoglobin value were excluded from the full analysis set, and patients with a major protocol violation of clinical or statistical relevance were excluded from the per protocol analysis set.

carried forward approach. Treatment and stratum (serum-ferritin (<100 versus ≥100 ng/mL) were used as factors and baseline value as a covariate. The mixed model for repeated measures (MMRM) was used to compare the average change in Hb concentration from baseline to Weeks 2, 4 and 6, change in serum-iron, TSAT, serum-ferritin and reticulocyte count from baseline to Weeks 1, 2, 4 and 6, and the change in QoL score from baseline to Weeks 4 and 6 with the use of treatment, visit, treatment*visit interactions, country, and stratum as factors and baseline values as covariates. The Proc MIXED procedure of SAS was used for the MMRM analysis with the model factor (visit*treatment estimate at the relevant week) and least-square means and estimate statements for treatment estimates and contrasts between the treatments, respectively.

The baseline characteristics and safety data were displayed descriptively. All tests were two-tailed and the significance level was 0.05.

RESULTS

Subjects

A total of 660 subjects were screened in the period 14 June 2011 to 10 September 2013, of whom 351 subjects were randomized 2 : 1 into Group A (234 subjects) and Group B (117 subjects). Group A was further subdivided into subgroups A1 (single dose, 117 subjects) and A2 (split dose, 117 subjects). The last patient visit was 28 October 2013.

Of the 351 subjects enrolled, 323 (92%) subjects completed the trial and 28 (8%) subjects discontinued. The details of patient disposition are summarized in Figure 1.

Patient demographics and baseline characteristics are summarized in Table 2 and baseline laboratory parameters are summarized in Table 3. Overall baseline characteristics in Groups A and B were comparable except for a higher

Table 2. Summary of baseline demographics and screening laboratory values for iron isomaltoside 1000 and iron sucrose, randomized population

Statistics/category	Treatment group		
	Iron isomaltoside 1000 ($n = 234$)	Iron sucrose ($n = 117$)	Overall ($N = 351$)
Age (years)			
n	233	117	350
Mean	60.13	59.50	59.92
SD	16.21	15.39	15.92
Median	63.00	62.00	62.00
Range (min : max)	(18 : 89)	(26 : 84)	(18 : 89)
Gender, n (%)			
Men	157 (67.1)	74 (63.2)	231 (65.8)
Women	76 (32.5)	43 (36.8)	119 (33.9)
Ethnic origin, n (%)			
Caucasian	154 (65.8)	74 (63.2)	228 (65.0)
Black	14 (6.0)	5 (4.3)	19 (5.4)
Asian	64 (27.4)	37 (31.6)	101 (28.8)
Others	1 (0.4)	1 (0.9)	2 (0.6)
BMI (kg/m^2)			
n	232	117	349
Mean	27.65	27.41	27.57
SD	6.77	6.34	6.62
Median	25.85	26.37	25.90
Range (min : max)	(15.3 : 55.8)	(17.1 : 44.3)	(15.3 : 55.8)
Mean dialysis time before entering the trial (years)			
n	233	117	350
Mean	3.46	3.59	3.50
SD	3.95	4.08	3.98
Median	2.19	2.37	2.23
Range (min : max)	(0.25 : 26.82)	(0.27 : 22.25)	(0.25 : 26.82)
Common concomitant illness, n (%)			
Diabetes mellitus	83 (35.5)	36 (30.8)	119 (33.9)
Hypertension arterial	160 (68.4)	87 (74.4)	247 (70.4)
Ischaemic heart disease	32 (13.7)	8 (6.8)	40 (11.4)
Haemoglobin (g/dL) at screening			
n	234	117	351
Mean (SD)	11.2 (0.66)	11.0 (0.76)	11.1 (0.69)
Median (min : max)	11.2 (9.5 : 12.5)	11.0 (9.5 : 12.5)	11.1 (9.5 : 12.5)
Transferrin saturation (%)			
n	234	117	351
Mean (SD)	21.6 (5.95)	22.6 (6.76)	21.9 (6.24)
Median (min : max)	21 (7.0 : 34.4)	23 (8.0 : 34.8)	22 (7.0 : 34.8)
Serum-ferritin (ng/mL) at screening			
n	234	117	351
Mean (SD)	367 (180)	384 (184)	373 (181)
Median (min : max)	362 (7.2 : 791)	376 (7.8 : 798)	367 (7.2 : 798)
C-reactive protein (ng/mL) at screening			
n	234	117	351
Mean (SD)	6.85 (7.33)	7.61 (10.1)	7.1 (8.37)
Median (min : max)	5 (0.37 : 49)	5 (0.42 : 78)	5 (0.37 : 78)

proportion of ischaemic heart disease at inclusion in Group A (32/234; 13.7%) compared with Group B (8/117; 6.8%) (Table 2).

Exposure to iron

All subjects, who were dosed, received a cumulative dose of 500 mg iron.

Efficacy results

Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL. The primary analysis was conducted on the FAS ($N = 341$) and PP analysis set ($N = 306$).

The primary analysis in both FAS and PP populations showed that the majority (>82%) of subjects treated with either iron isomaltoside 1000 (FAS: 187/226; PP: 167/199) or iron sucrose (FAS: 95/115; PP: 88/107) were able to maintain Hb between 9.5 and 12.5 g/dL at Week 6 (Figure 2). The test for non-inferiority showed that iron isomaltoside 1000 was non-inferior to iron sucrose (FAS: P = 0.01; PP: P = 0.006) (Figure 2). Non-inferiority was also shown when comparing subgroup A2 (FAS: 95/113; PP: 83/97) to B (FAS: P = 0.01; PP: P = 0.006), whereas subgroup A1 only showed non-inferiority in the PP population (84/102) but not in the FAS population (92/113) when compared with B (FAS: P = 0.06; PP: P = 0.04).

Change in laboratory parameters. The change in laboratory parameters (secondary outcomes) was conducted on the FAS (*N* = 341).

Table 3. Baseline laboratory parameters, FAS

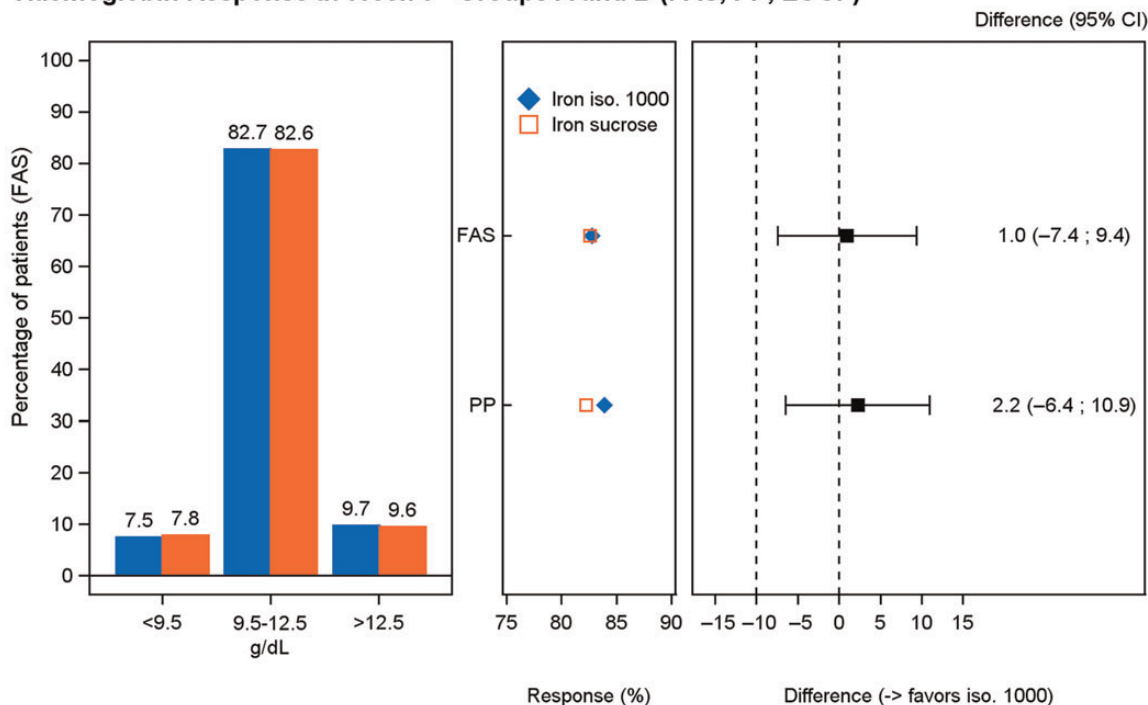| Parameter	Iron isomaltoside 1000 (*n* = 226)	Iron sucrose (*n* = 115)
Haemoglobin (g/dL)		
n	225	114
Mean (SD)	11.20 (0.83)	11.08 (0.93)
Median (min : max)	11.21 (9.1 : 15.6)	11.00 (8.4 : 14.6)
Serum-iron (µg/dL)[a]		
n	225	113
Mean (SD)	57.87 (22.48)	60.22 (22.43)
Median (min : max)	54.19 (5.03 : 172.07)	59.00 (14.00 : 122.00)
Transferrin saturation (%)		
n	225	113
Mean (SD)	22.20 (17.90)	22.57 (8.49)
Median (min : max)	20.00 (2.0 : 265.0)	22.00 (5.5 : 48.2)
Serum-ferritin (ng/mL)		
n	225	114
Mean (SD)	350.88 (186.17)	357.74 (192.98)
Median (min : max)	338.00 (9.5 : 997.6)	333.50 (12.4 : 986.7)
Reticulocyte count (%)		
n	216	110
Mean (SD)	1.33 (0.6)	1.26 (0.55)
Median (min : max)	1.30 (0.1 : 3.1)	1.25 (0.1 : 2.6)

[a]Conversion factor for serum-iron: µg/dL × 0.179 = µmol/L.

The estimated effect size for the laboratory parameters including its precision are shown for Group A compared with B in Table 4, Group A1 compared with B in Table 5, Group A2 compared with B in Table 6 and Group A1 compared with A2 in Table 7.

Change in Hb concentration and reticulocytes. The Hb levels and absolute change in Hb in the different treatment groups are shown in Figures 3 and 4. There was no statistical significant change in Hb concentration from baseline to Weeks 2, 4 and Week 6 between Groups A and B (Table 4, Figure 5). Similar results were observed when subgroups A1 and A2 were compared (Table 7) and when subgroups A1 and A2 were compared with Group B except at Week 2 where the increase in Hb concentration from baseline was significantly higher in subgroup A1 compared with Group B (P = 0.05) (Tables 5 and 6, Figure 6).

There was a statistically significant increase in reticulocyte count at Week 1 in Group A compared with Group B (P < 0.001), and similar findings were found when comparing subgroups A1 and A2 to Group B (A1 versus B: P < 0.001, A2 versus B: P = 0.02) (Tables 4–6). No statistically significant changes in reticulocyte counts were observed from baseline to Weeks 2, 4 and 6 between Groups A and B (Table 4) and no statistically significant changes in reticulocyte counts were observed between subgroups A1 and A2 (Table 7).

Haemoglobin Response at Week 6 - Groups A and B (FAS, PP, LOCF)

Response: Haemoglobin in 9.5 - 12.5 g/dL (both included). Non-inferiority margin: -10 percentage-points
Estimates from generalised linear model using the identity link function with treatment and stratum as factors, and baseline value as covariate
FAS: Full Analysis Set, PP: Per-protocol Analysis Set, LOCF: Last observation carried forward, CI: Confidence interval
Iron iso. 1000 = Iron isomaltoside 1000

FIGURE 2: Hb response at Week 6.

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Table 4. Laboratory parameters: estimated effect size and its precision, Group A versus B, FAS

Laboratory parameter, time point (number of subjects)	Iron isomaltoside 1000 (Group A), least-square mean estimate[a]	Iron sucrose (Group B), least-square mean estimate[a]	Difference estimates (95% CI)	P-value
Haemoglobin (g/dL)				
Week 2 (Group A: 219, Group B: 115)	0.107	−0.00664	0.114 (−0.0314;0.259)	0.1
Week 4 (Group A: 213, Group B: 114)	0.0631	0.00852	0.0546 (−0.113;0.223)	0.5
Week 6 (Group A: 216, Group B: 113)	−0.00694	−0.0277	0.0208 (−0.204;0.246)	0.9
Serum-iron (μg/dL)				
Week 1 (Group A: 221, Group B: 112)	7.27	4.04	3.24 (−1.1;7.57)	0.1
Week 2 (Group A: 220, Group B: 115)	5.39	3.29	2.1 (−4.45;8.65)	0.5
Week 4 (Group A: 212, Group B: 114)	3.72	5.72	−2 (−7.06;3.07)	0.4
Week 6 (Group A: 216, Group B: 113)	4.08	4.04	0.0368 (−5.39;5.46)	0.9
Transferrin saturation (%)				
Week 1 (Group A: 221, Group B: 111)	0.453	6.98	−6.52 (−21.4;8.33)	0.4
Week 2 (Group A: 220, Group B: 115)	0.137	−1.06	1.2 (−1.35;3.75)	0.4
Week 4 (Group A: 212, Group B: 114)	−0.631	0.366	−0.997 (−3.09;1.1)	0.3
Week 6 (Group A: 216, Group B: 113)	−0.0497	−0.029	−0.0207 (−2.12;2.08)	0.9
Serum-ferritin (ng/mL)				
Week 1 (Group A: 221, Group B: 113)	147	39.1	108 (88;128)	<0.001
Week 2 (Group A: 220, Group B: 115)	135	11.3	123 (96.4;150)	<0.001
Week 4 (Group A: 212, Group B: 114)	126	76.4	49.3 (18.2;80.5)	0.002
Week 6 (Group A: 216, Group B: 114)	130	145	−15.1 (−54.2;24.1)	0.4
Reticulocyte count (%)				
Week 1 (Group A: 212, Group B: 108)	0.165	0.0106	0.154 (0.0664;0.242)	<0.001
Week 2 (Group A: 211, Group B: 111)	0.0933	0.0494	0.0439 (−0.0475;0.135)	0.3
Week 4 (Group A: 204, Group B: 110)	0.0949	0.0647	0.0302 (−0.0614;0.122)	0.5
Week 6 (Group A: 207, Group B: 109)	0.105	0.0327	0.0727 (−0.028;0.173)	0.2

Conversion factor for serum-iron: μg/dL × 0.179 = μmol/L.
[a]Least-square means from repeated measures model with treatment, visit, stratum (serum-ferritin <100 versus ≥100 ng/mL) and country as factors, baseline value as a covariate and the interaction between treatment and visit.

Table 5. Laboratory parameters: estimated effect size and its precision, Group A1 versus B, FAS

Laboratory parameter, time point (number of subjects)	Iron isomaltoside 1000 (Group A1), least-square mean estimate[a]	Iron sucrose (Group B), least-square mean estimate[a]	Difference estimates (95% CI)	P-value
Haemoglobin (g/dL)				
Week 2 (Group A1: 110, Group B: 115)	0.155	−0.00664	0.162 (0.00389;0.32)	0.05
Week 4 (Group A1: 109, Group B: 114)	0.0958	0.00852	0.0872 (−0.109;0.284)	0.4
Week 6 (Group A1: 110, Group B: 113)	−0.0256	−0.0277	0.00213 (−0.245;0.25)	0.9
Serum-iron (μg/dL)				
Week 1 (Group A1: 112, Group B: 112)	15.1	4.04	11.1 (5.72;16.5)	<0.001
Week 2 (Group A1: 111, Group B: 115)	6.64	3.29	3.35 (−3.66;10.4)	0.3
Week 4 (Group A1: 109, Group B: 114)	5.6	5.72	−0.114 (−5.65;5.43)	0.9
Week 6 (Group A1: 110, Group B: 113)	2.64	4.04	−1.4 (−7.41;4.6)	0.6
Transferrin saturation (%)				
Week 1 (Group A1: 112, Group B: 111)	3.79	6.98	−3.19 (−18.1;11.7)	0.7
Week 2 (Group A1: 111, Group B: 115)	1.53	−1.06	2.59 (−0.997;6.19)	0.2
Week 4 (Group A1: 109, Group B: 114)	0.211	0.366	−0.155 (−2.53;2.21)	0.9
Week 6 (Group A1: 110, Group B: 113)	−0.896	−0.029	−0.867 (−3.3;1.57)	0.5
Serum-ferritin (ng/mL)				
Week 1 (Group A1: 112, Group B: 113)	252	39.1	213 (184;242)	<0.001
Week 2 (Group A1: 111, Group B: 115)	236	11.3	225 (185;265)	<0.001
Week 4 (Group A1: 109, Group B: 114)	155	76.4	78.6 (38;119)	<0.001
Week 6 (Group A1: 110, Group B: 114)	103	145	−41.8 (−83.6;0.0552)	0.05
Reticulocyte count (%)				
Week 1 (Group A1: 107, Group B: 108)	0.209	0.0106	0.199 (0.0863;0.311)	<0.001
Week 2 (Group A1: 106, Group B: 111)	0.105	0.0494	0.0559 (−0.0546;0.166)	0.3
Week 4 (Group A1: 105, Group B: 110)	0.087	0.0647	0.0223 (−0.0959;0.14)	0.7
Week 6 (Group A1: 106, Group B: 109)	0.101	0.0327	0.0687 (−0.0575;0.195)	0.3

Conversion factor for serum-iron: μg/dL × 0.179 = μmol/L.
[a]Least-square means from repeated measures model with treatment, visit, stratum (serum-ferritin <100 versus ≥100 ng/mL) and country as factors, baseline value as a covariate and the interaction between treatment and visit.

Table 6. Laboratory parameters: estimated effect size and its precision, Group A2 versus B, FAS

Laboratory parameter, time point (number of subjects)	Iron isomaltoside 1000 (Group A2), least-square mean estimate[a]	Iron sucrose (Group B), least-square mean estimate[a]	Difference estimates (95% CI)	P-value
Haemoglobin (g/dL)				
Week 2 (Group A2: 109, Group B: 115)	0.0589	−0.00664	0.0655 (−0.115;0.246)	0.5
Week 4 (Group A2: 104, Group B: 114)	0.0304	0.00852	0.0219 (−0.193;0.237)	0.8
Week 6 (Group A2: 106, Group B: 113)	0.0117	−0.0277	0.0395 (−0.246;0.325)	0.8
Serum-iron (µg/dL)				
Week 1 (Group A2: 109, Group B: 112)	−0.591	4.04	−4.63 (−9.65;0.397)	0.07
Week 2 (Group A2: 109, Group B: 115)	4.14	3.29	0.85 (−6.42;8.12)	0.8
Week 4 (Group A2: 103, Group B: 114)	1.84	5.72	−3.88 (−10.1;2.32)	0.2
Week 6 (Group A2: 106, Group B: 113)	5.51	4.04	1.48 (−5.55;8.5)	0.7
Transferrin saturation (%)				
Week 1 (Group A2: 109, Group B: 111)	−2.89	6.98	−9.86 (−24.7;5.01)	0.2
Week 2 (Group A2: 109, Group B: 115)	−1.26	−1.06	−0.197 (−2.64;2.25)	0.9
Week 4 (Group A2: 103, Group B: 114)	−1.47	0.366	−1.84 (−4.31;0.634)	0.1
Week 6 (Group A2: 106, Group B: 113)	0.797	−0.029	0.826 (−1.82;3.48)	0.5
Serum-ferritin (ng/mL)				
Week 1 (Group A2: 109, Group B: 113)	41.8	39.1	2.62 (−16.3;21.6)	0.8
Week 2 (Group A2: 109, Group B: 115)	33.3	11.3	21.9 (−4.33;48.2)	0.1
Week 4 (Group A2: 103, Group B: 114)	96.5	76.4	20.1 (−14.3;54.4)	0.3
Week 6 (Group A2: 106, Group B: 114)	157	145	11.7 (−34.5;57.8)	0.6
Reticulocyte count (%)				
Week 1 (Group A2: 105, Group B: 108)	0.12	0.0106	0.109 (0.0154;0.203)	0.02
Week 2 (Group A2: 105, Group B: 111)	0.0813	0.0494	0.0319 (−0.0728;0.137)	0.5
Week 4 (Group A2: 99, Group B: 110)	0.103	0.0647	0.0381 (−0.0659;0.142)	0.5
Week 6 (Group A2: 101, Group B: 109)	0.109	0.0327	0.0768 (−0.0417;0.195)	0.2

Conversion factor for serum-iron: µg/dL × 0.179 = µmol/L.

[a]Least-square means from repeated measures model with treatment, visit, stratum (serum-ferritin <100 versus ≥100 ng/mL) and country as factors, baseline value as a covariate and the interaction between treatment and visit.
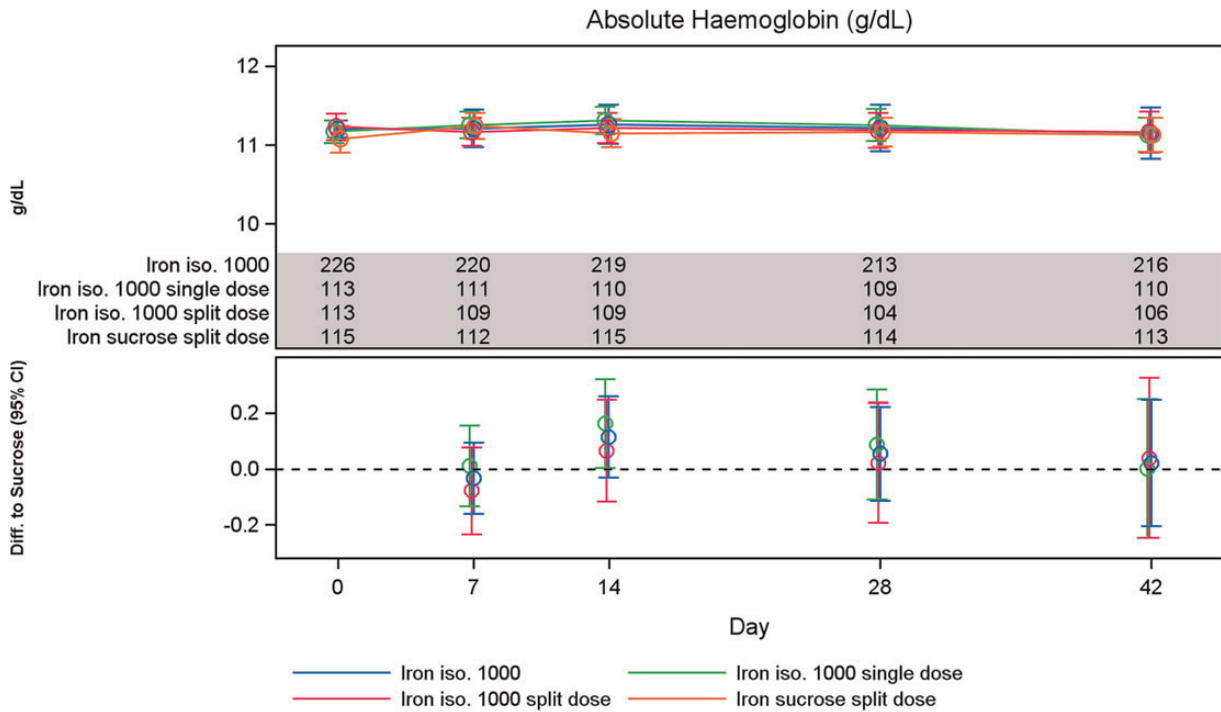
Table 7. Laboratory parameters: estimated effect size and its precision, Group A1 versus A2, FAS

Laboratory parameter, time point (number of subjects)	Iron isomaltoside 1000 (Group A1), least-square mean estimate[a]	Iron isomaltoside 1000 (Group A2), least-square mean estimate[a]	Difference estimates (95% CI)	P-value
Haemoglobin (g/dL)				
Week 2 (Group A1: 110, Group A2: 109)	0.155	0.0589	0.0966 (−0.0797;0.273)	0.3
Week 4 (Group A1: 109, Group A2: 104)	0.0958	0.0304	0.0654 (−0.171;0.302)	0.6
Week 6 (Group A1: 110, Group A2: 106)	−0.0256	0.0117	−0.0373 (−0.325;0.25)	0.8
Serum-iron (µg/dL)				
Week 1 (Group A1: 112, Group A2: 109)	15.1	−0.591	15.7 (10;21.5)	<0.001
Week 2 (Group A1: 111, Group A2: 109)	6.64	4.14	2.5 (−3.2;8.21)	0.4
Week 4 (Group A1: 109, Group A2: 103)	5.6	1.84	3.77 (−2.2;9.73)	0.2
Week 6 (Group A1: 110, Group A2: 106)	2.64	5.51	−2.88 (−10.1;4.39)	0.4
Transferrin saturation (%)				
Week 1 (Group A1: 112, Group A2: 109)	3.79	−2.89	6.68 (4.24;9.11)	<0.001
Week 2 (Group A1: 111, Group A2: 109)	1.53	−1.26	2.79 (−0.633;6.22)	0.1
Week 4 (Group A1: 109, Group A2: 103)	0.211	−1.47	1.68 (−0.751;4.12)	0.2
Week 6 (Group A1: 110, Group A2: 106)	−0.896	0.797	−1.69 (−4.56;1.18)	0.2
Serum-ferritin (ng/mL)				
Week 1 (Group A1: 112, Group A2: 109)	252	41.8	210 (183;238)	<0.001
Week 2 (Group A1: 111, Group A2: 109)	236	33.3	203 (162;244)	<0.001
Week 4 (Group A1: 109, Group A2: 103)	155	96.5	58.5 (16.6;100)	0.006
Week 6 (Group A1: 110, Group A2: 106)	103	157	−53.4 (−93.9;−13)	0.01
Reticulocyte count (%)				
Week 1 (Group A1: 107, Group A2: 105)	0.209	0.12	0.0891 (−0.021;0.199)	0.1
Week 2 (Group A1: 106, Group A2: 105)	0.105	0.0813	0.024 (−0.0894;0.138)	0.7
Week 4 (Group A1: 105, Group A2: 99)	0.087	0.103	−0.0158 (−0.142;0.11)	0.8
Week 6 (Group A1: 106, Group A2: 101)	0.101	0.109	−0.00807 (−0.146;0.13)	0.9

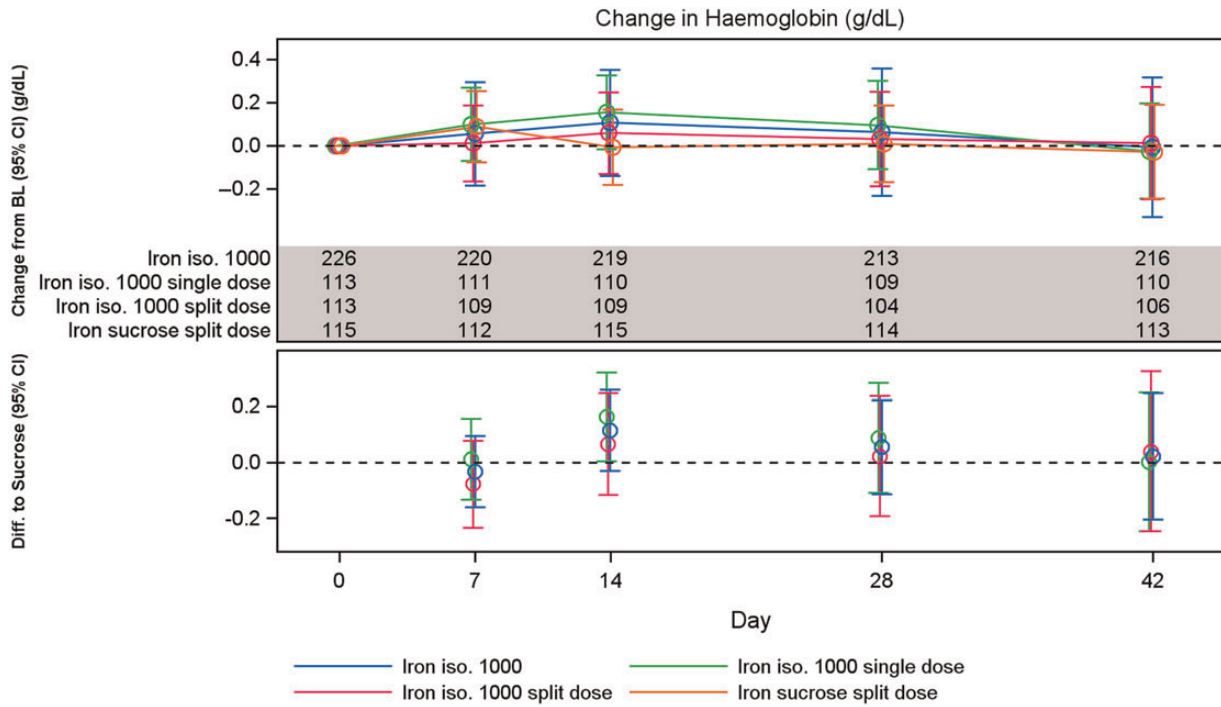Conversion factor for serum-iron: µg/dL × 0.179 = µmol/L.

[a]Least-square means from repeated measures model with treatment, visit, stratum (serum-ferritin <100 versus ≥100 ng/mL) and country as factors, baseline value as a covariate and the interaction between treatment and visit.

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FIGURE 3: Hb concentration over time by treatment group.

FIGURE 4: Change in Hb concentration over time by treatment group.

Change in concentrations of serum-iron, TSAT, and serum-ferritin. There was an increase in serum-iron and TSAT concentration from baseline to Weeks 1, 2, 4 and 6 in both Groups A and B; however, no statistically significant changes were observed between the treatment groups (Table 4). At Week 1, there was a statistically significant higher increase in serum-iron in subgroup

Haemoglobin Over Time, by Treatment Group - Groups A and B

Least square means (95% CI) from a repeated measures analysis with strata and country as factors, treatment*week interaction, and baseline value as covariate
Iron iso. 1000 = Iron isomaltoside 1000

FIGURE 5: Hb over time by treatment group.

A1 compared with Group B (P < 0.001) (Table 5) and in subgroup A1 compared with subgroup A2 (P < 0.001) (Table 7). At Week 1, there was a statistically significant higher increase in TSAT in subgroup A1 compared with subgroup A2 (P < 0.001) (Table 7). Interestingly, Group B demonstrated a very wide variation in TSAT at 1 week compared with Group A (Figure 6).

There was a statistically significant increase in serum-ferritin concentration from baseline to Weeks 1, 2 and 4 in Group A compared with Group B (Weeks 1 and 2: P < 0.001; Week 4: P = 0.002) (Table 4). This difference was only evident in Group A1 (P < 0.001) but not in Group A2 (Tables 5 and 6, Figure 6). No statistically significant change in serum-ferritin concentration was observed from baseline to Week 6 between Groups A and B (Table 4). There was a statistically significant higher increase in serum-ferritin in subgroup A1 compared with subgroup A2 at Weeks 1, 2 and 4 (Weeks 1 and 2: P < 0.001; Week 4: P = 0.007) and at Week 6 it was vice versa (P = 0.01) (Table 7). A total of 9/113 (8%) and 4/113 (4%) experienced ferritinemia (i.e. >1000 ng/mL) in Groups A1 and A2, respectively. There was no statistically significant difference between the groups (P = 0.25).

Change in total QoL. The change in QoL (secondary outcomes) was conducted on the FAS (N = 341).

There was no statistically significant difference in the patient's energy level, ability to do daily activities and overall QoL between Groups A and B (Supplementary data, Table 1).

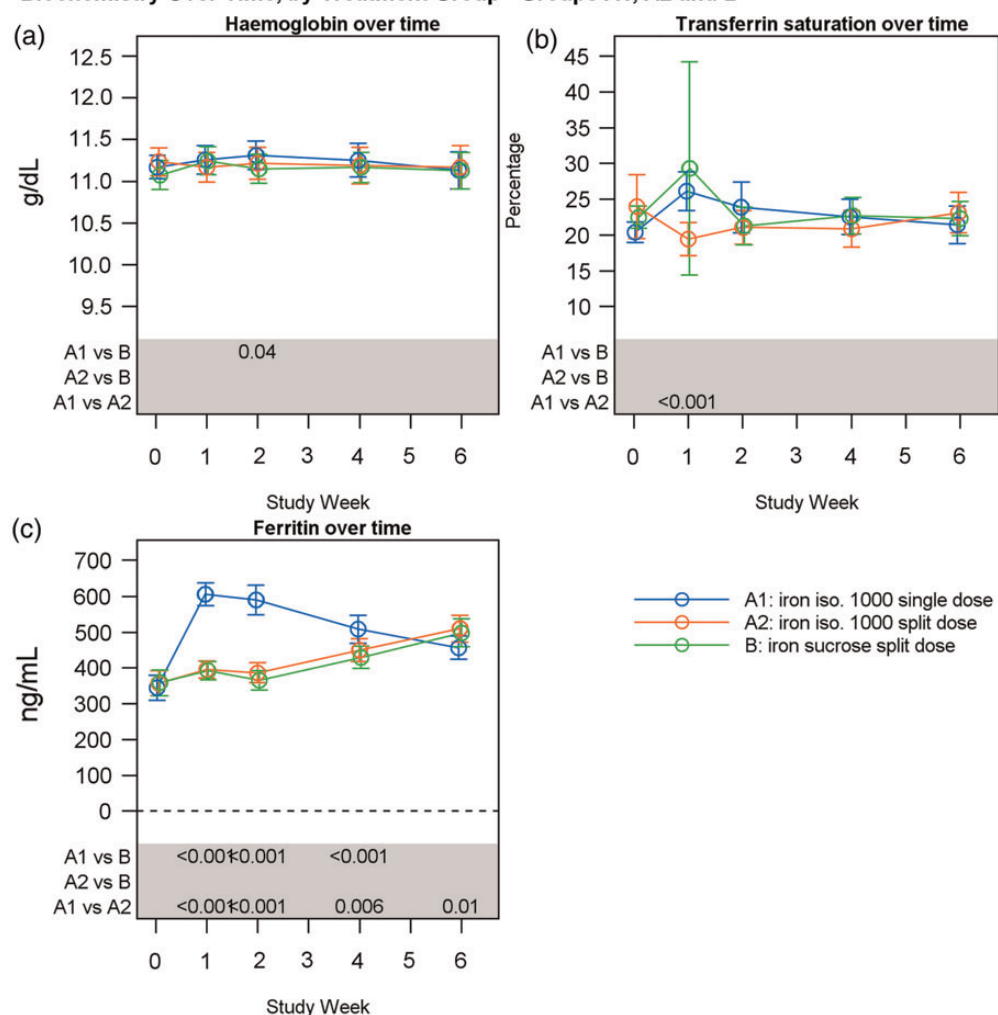**Safety.** All safety analyses were conducted on the safety analysis set (N = 344).

For both iron isomaltoside 1000 and iron sucrose, the majority of the adverse events (AEs) were mild or moderate and unrelated to the trial drug. The proportion of subjects with AEs [Group A: 110/230 (47.8%); Group B: 47/114 (41.2%)] was similar (Table 8). Related AEs (i.e. ADR) were observed in 12/230 (5.2%) subjects in Group A and 3/114 (2.6%) subjects in Group B. One patient reported three ADRs. Hence, there was a total of 12 ADRs in 230 subjects (5.2%) in Group A [drug intolerance, hypersensitivity, dyspepsia, malaise, muscle spasms and paraesthesia in subgroup A1 and drug intolerance, anxiety, constipation, pruritus (2 events) and urticaria in subgroup A2] and 5 in 114 subjects (4.4%) in Group B (dry mouth, dyspnoea, chills, staphylococcal bacteraemia and limb discomfort). Of these ADRs, three were reported as serious ADRs (Group A: 1/230 (0.4%); Group B: 2/114 (1.8%); hypersensitivity in Group A and staphylococcal bacteraemia and dyspnoea in Group B. The dyspnoea and hypersensitivity reactions both occurred during the injections and were both treated as hypersensitivity reactions with administration of antihistamine and corticosteroid treatment. Vital signs were not affected and both subjects recovered completely within a short time period.

Three subjects in Group A died during the trial and additional two subjects died between screening and randomization without being exposed to trial drug. In all cases, these events were deemed not related by the investigator and caused by other factors either in the patient's medical history/condition or in a single case a car accident. The observed mortality was in line with the expected mortality in this population in this time frame.

No differences in safety findings relating to vital signs or safety parameters between groups were observed. A low number of subjects treated with both iron isomaltoside 1000 and iron sucrose [3/230 (1.3%) versus 3/114 (2.6%)] reported hypophosphatemia defined as <2 mg/dL; however, no event was considered an AE.

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Biochemistry Over Time, by Treatment Group - Groups A1, A2 and B

Least squares means (95% CI) from a repeated measures analysis with strata and country as factors, treatment*week interaction, and baseline value as covariate
Iron iso. 1000 = Iron isomaltoside 1000
P-values < 0.05 are indicated

FIGURE 6: Hb, serum-ferritin and TSAT over time by treatment group.

Table 8. Summary of AEs for iron isomaltoside 1000 (single and split dose) and iron sucrose

Number of subjects	Iron isomaltoside 1000, single dose (n = 114)	Iron isomaltoside 1000, split dose (n = 116)	Iron sucrose (n = 114)
AEs, n (%)	51 (45)	59 (51)	47 (41)
Adverse drug reaction, n (%)	6 (5)	6 (5)	3 (3)
Serious AEs, n (%)	9 (8)	13 (11)	6 (5)
Serious adverse drug reactions, n (%)	1 (<1)	–	2 (2)
Suspected unexpected serious adverse reaction, n (%)	–	–	1 (<1)

DISCUSSION

The majority (82%) of subjects maintained a Hb level between 9.5 and 12.5 g/dL at Week 6, confirming that both iron preparations exhibited similar efficacy with equivalent doses. A total of 18% of the patients in both treatment Groups A and B had Hb levels outside the target range of 9.5–12.5 g/dL at Week 6, of which ~7.5% had a Hb <9.5 g/dL and 9.6% had a Hb >12.5

g/dL (Figure 2). The mean Hb at baseline did not differ between the treatment groups and remained stable within the target range throughout the study as shown in Figure 3. The reason that some individual patients had an increase in Hb levels is probably related to the effect of iron therapy leading to improved erythron production of Hb in the 9.6% of the patients, whereas a decrease in Hb could be related to a number of factors such as bleeding, loss of a dialysis circuit from clotting and insufficient iron repletion therapy. It should be kept in mind that

peripheral-iron blood indices of iron storage transport and handling have limited utility in identifying depletion of bone marrow iron stores. Even in patients with adequate bone marrow iron stores, it is sometimes possible to obtain an increase in Hb levels following iron therapy. However, this quantitative effect is lower in patients who are not iron deficient [16].

The mean serum-iron and TSAT concentrations increased from baseline to Week 6 in both treatment groups with no differences between them. Serum-ferritin initially increased more with the 500 mg single bolus compared with split dosing as one would anticipate. The maximal mean rise was observed at Week 1 with a rise up to ∼600 ng/mL followed by a steady fall towards baseline during the 6-week period. In contrast, a steady increase was observed on split dosing also by Week 6. The clinical significance of these findings for optimal dosing guidance remain speculative, but consistent with current clinical practice guidelines, serum-ferritin levels are generally lower than those found in patients with haemochromatosis where relevant tissue iron deposition starts to occur [17]. Currently, based on data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) Practice Monitor of 120 dialysis facilities in the USA in over a quarter of these facilities the ferritin levels exceed 800 ng/mL. Indeed, serum-ferritin concentration was at least 800 ng/mL in 34% of patients, and was >1200 ng/mL in 11% of patients [18].

A limitation of the trial is that it does not provide long-term safety data. However, it seems that the short-term safety profile of iron isomaltoside 1000 and iron sucrose are similar. The majority of the AEs in both treatment groups was mild or moderate and was unrelated to the trial drug. Three serious ADRs were reported, one on iron isomaltoside 1000 (0.4% of subjects) and two on iron sucrose (1.8% of subjects). Although iron isomaltoside 1000 demonstrated a lower percentage of serious ADRs, the trial was not powered to examine potential systematic differences in serious ADRs. Hypersensitivity reactions were rare in both groups with only one reaction requiring intervention with antihistamine and steroid in both groups. Vital signs were not affected and both subjects recovered. The present findings were analogous to other studies where both iron isomaltoside 1000 and iron sucrose showed a good safety profile in CKD patients [19, 20, 21].

An event of staphylococcal infection was considered possibly related to iron sucrose. Based on the literature, the arguments supporting relationship between IV iron and risk of infections are controversial. Several small studies in populations with CKD suggest an increased infection risk associated with IV iron therapy [22]. This association has been linked to labile iron acting as a necessary growth factor for pathogen growth [23, 24]. However, other epidemiological studies have failed to find an association between IV iron administration and infectious complications [25]. In addition, CKD is *per se* also associated with significant major infectious complications, which occur at rates 3–4 times the general population [26–28].

This trial only studied short-term safety. In relation to long-term safety it has recently been reported that IV iron isomaltoside 1000 and iron sucrose differ in their stability, with iron sucrose purported to release more labile iron [12]. Since some studies have linked labile iron to infections and cardiovascular

morbidity, the long-term safety profile between the products might differ [29, 30].

In conclusion, this randomized trial demonstrated non-inferiority of iron isomaltoside 1000 in comparison with iron sucrose in maintaining Hb levels in subjects on haemodialysis. The safety profile of iron isomaltoside 1000 was comparable with iron sucrose and both preparations were equally tolerated with a similar short-term safety profile.

CONFLICT OF INTEREST STATEMENT

All investigators/institutions received a fee per subject. S.B. received speaker and consultancy fees from Pharmacosmos A/S. P.A.K. received speaker and consultancy fees and assistance with travel from Pharmacosmos A/S, Vifor and Takeda. J.K.'s institution received research support for conducting the trial. P.A. has no further disclosure to the trial. J.H.C.'s institution received research support for conducting the trial as well as they received research support from other IV iron manufacturers. A.M.E. has no further disclosure to the trial. L.L.T. is employed by Pharmacosmos A/S. I.C.M. received consultancy fees and honoraria from Pharmacosmos A/S, as well as from other IV iron manufacturers. D.W.C. is a consultant to Pharmacosmos A/S, Vifor and Keryx, and was previously a consultant and speaker for Watson (now Actavis) and Sanofi Aventis.

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