Clinical trial results:
A phase III, randomised, comparative, open-label study of intravenous iron isomaltoside 1000 (Monofer®) administered as maintenance therapy by single or repeated bolus injections in comparison with intravenous iron sucrose in subjects with stage 5 chronic kidney disease on dialysis therapy (CKD-5D)

Summary

EudraCT number	2010-023471-26
Trial protocol	GB SE DK PL
Global end of trial date	28 October 2013

Results information

Result version number	v1
This version publication date	16 March 2016
First version publication date	15 July 2015

Trial information

Trial identification

Sponsor protocol code	P-Monofer-CKD-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01222884
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharmacosmos A/S
Sponsor organisation address	Roervangsvej 30, Holbaek, Denmark, Dk-4300
Public contact	Clinical trial disclosure desk, Pharmacosmos A/S, 045 59485935, trial@pharmacosmos.com
Scientific contact	Clinical trial disclosure desk, Pharmacosmos A/S, 045 59485935, trial@pharmacosmos.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 October 2013
Global end of trial reached?	Yes
Global end of trial date	28 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective of the study was to demonstrate that IV iron isomaltoside 1000 is non-inferior to IV iron sucrose determined as ability to maintain haemoglobin (Hb) between 9.5 and 12.5 g/dL in subjects with CKD-5D who were on maintenance iron therapy.

Protection of trial subjects:

The protocol and amendments were approved by local ethics committees/Institutional Review Boards and competent authorities. The trial was conducted in accordance with good clinical practice and the Declaration of Helsinki. Informed consent was obtained in writing prior to any trial-related activities.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 June 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	United Kingdom: 187
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	India: 72
Country: Number of subjects enrolled	Romania: 26
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Switzerland: 19
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	351
EEA total number of subjects	247

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	195
From 65 to 84 years	146
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

Subjects were screened in the period 14 June 2011 to 10 September 2013. 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.

Pre-assignment

Screening details:

Subjects ≥ 18 years of age with a diagnosis of CKD and on haemodialysis therapy for at least 90 days, Hb between 9.5 and 12.5 g/dL (inclusive both values) both at screening visit 1a and screening visit 1b, serum-ferritin < 800 ng/mL, TSAT < 35%, and receiving ESA treatment with stable dose for the previous 4 weeks prior to screening were enrolled.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A, iron isomaltoside 1000

Arm description:

All subjects received a cumulative dose of 500 mg iron isomaltoside 1000. Subjects in subgroup A1 were administered iron isomaltoside 1000 as a single undiluted IV bolus injection of 500 mg over approximately 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 week 2 and 4 as IV bolus injections over approximately 2 min.

Arm type	Experimental
Investigational medicinal product name	Iron isomaltoside 1000
Investigational medicinal product code	ATC code: B03AC
Other name	Monofer, Monover, Monofar, Monoferro
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

All subjects received a cumulative dose of 500 mg iron isomaltoside 1000. Subjects in subgroup A1 were administered iron isomaltoside 1000 as a single undiluted IV bolus injection of 500 mg over approximately 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 week 2 and 4 as IV bolus injections over approximately 2 min.

Iron isomaltoside 1000 is available as a dark brown, non-transparent aqueous solution for injection/infusion containing 100 mg iron/mL with pH between 5.0 and 7.0.

Arm title	Group B, iron sucrose

Arm description:

All subjects received a cumulative dose of 500 mg iron sucrose.
Subjects in group B were administered undiluted iron sucrose in split doses of 100 mg at baseline and 200 mg each at week 2 and 4.

Arm type	Active comparator
Investigational medicinal product name	Iron sucrose
Investigational medicinal product code	ATC code: B03AB02,B03AC02
Other name	Venofer
Pharmaceutical forms	Concentrate for solution for infusion, Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects in group B were administered undiluted iron sucrose in split doses of 100 mg at baseline and 200 mg each at week 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.

Number of subjects in period 1	Group A, iron isomaltoside 1000	Group B, iron sucrose
Started	234	117
Completed	210	113
Not completed	24	4
Adverse event, serious fatal	3	-
Consent withdrawn by subject	6	2
Physician decision	1	-
Subject decided to go on holiday for 8 we	1	-
Kidney transplantation	1	-
Patient had been given IV iron by dialysis staff	1	-
Adverse event, non-fatal	8	1
Did not fulfil the inclusion/exclusion criteria	3	-
Transplant	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Group A, iron isomaltoside 1000
Reporting group description:	
All subjects received a cumulative dose of 500 mg iron isomaltoside 1000. Subjects in subgroup A1 were administered iron isomaltoside 1000 as a single undiluted IV bolus injection of 500 mg over approximately 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 week 2 and 4 as IV bolus injections over approximately 2 min.	
Reporting group title	Group B, iron sucrose
Reporting group description:	
All subjects received a cumulative dose of 500 mg iron sucrose. Subjects in group B were administered undiluted iron sucrose in split doses of 100 mg at baseline and 200 mg each at week 2 and 4.	

Reporting group values	Group A, iron isomaltoside 1000	Group B, iron sucrose	Total
Number of subjects	234	117	351
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age is calculated by subtracting the screening visit date with the birth date.			
Units: years			
arithmetic mean	60.2	59.5	
standard deviation	± 16.2	± 15.4	-
Gender categorical			
Units: Subjects			
Female	76	43	119
Male	158	74	232

Subject analysis sets	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population (N=344) included all subjects who were randomized and received at least one dose of the trial drug.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (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.

Subject analysis set title	Per protocol (PP) analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population (N=306) included all subjects in the FAS who did not have any major protocol deviation of clinical or statistical relevance.

Reporting group values	Safety analysis set	Full analysis set (FAS)	Per protocol (PP) analysis set
Number of subjects	344	341	306
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age is calculated by subtracting the screening visit date with the birth date.			
Units: years			
arithmetic mean	60	60.1	59.6
standard deviation	± 16	± 15.9	± 15.9
Gender categorical Units: Subjects			
Female	117	117	100
Male	227	224	206

End points

End points reporting groups

Reporting group title	Group A, iron isomaltoside 1000

Reporting group description:

All subjects received a cumulative dose of 500 mg iron isomaltoside 1000. Subjects in subgroup A1 were administered iron isomaltoside 1000 as a single undiluted IV bolus injection of 500 mg over approximately 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 week 2 and 4 as IV bolus injections over approximately 2 min.

Reporting group title	Group B, iron sucrose

Reporting group description:

All subjects received a cumulative dose of 500 mg iron sucrose.
Subjects in group B were administered undiluted iron sucrose in split doses of 100 mg at baseline and 200 mg each at week 2 and 4.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population (N=344) included all subjects who were randomized and received at least one dose of the trial drug.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (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.

Subject analysis set title	Per protocol (PP) analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population (N=306) included all subjects in the FAS who did not have any major protocol deviation of clinical or statistical relevance.

Primary: Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at week 6, FAS

End point title	Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at week 6, FAS

End point description:

Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at week 6.

The analysis was performed on the FAS.

End point type	Primary

End point timeframe:

Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at week 6.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	115		
Units: Proportion of subjects				
Responder	187	95		

Non-responder	39	20		

Statistical analyses

Statistical analysis title	Non-inferiority tested by risk difference

Statistical analysis description:

A generalised 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 carried forward approach.
The number of subjects may differ from the analysis population if data is missing.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.0106 [2]
Method	Risk differences
Parameter estimate	Risk difference (RD)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	9.4

Notes:

[1] - Treatment and stratum (serum-ferritin (<100 versus ≥100 ng/mL) were used as factors and baseline value as a covariate.
With a 2:1 randomisation, a two-sided significance level of 0.05, and a non-inferiority margin of 10 % points, there was approximately 80 % power to demonstrate non-inferiority with 214 subjects in group A and 107 subjects in group B.
[2] - As the trial was designed to demonstrate non-inferiority, the analyses of FAS and PP population would lead to similar conclusions and therefore the analyses for both analysis sets needed to be powered properly.

Primary: Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at week 6, PP

End point title	Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at week 6, PP

End point description:

Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at week 6.

The analysis was performed on the PP analysis set.

End point type	Primary

End point timeframe:

Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at week 6.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	107		
Units: Proportion of subjects				
Responder	167	88		
Non-responder	32	19		

Statistical analyses

Statistical analysis title	Non-inferiority tested by risk difference

Statistical analysis description:

A generalised 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 carried forward approach.
The number of subjects may differ from the analysis population if data is missing.

Comparison groups	Group B, iron sucrose v Group A, iron isomaltoside 1000
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.0057 [4]
Method	Risk difference
Parameter estimate	Risk difference (RD)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	10.9

Notes:

[3] - Treatment and stratum (serum-ferritin (<100 versus ≥100 ng/mL) were used as factors and baseline value as a covariate. With a 2:1 randomisation, a two-sided significance level of 0.05, and a non-inferiority margin of 10 % points, there was approximately 80 % power to demonstrate non-inferiority with 214 subjects in group A and 107 subjects in group B.
[4] - As the trial was designed to demonstrate non-inferiority, the analyses of FAS and PP population would lead to similar conclusions and therefore the analyses for both analysis sets needed to be powered properly.

Secondary: Change in Hb concentration from baseline to week 2

End point title	Change in Hb concentration from baseline to week 2

End point description:

Change in Hb concentration from baseline to week 2.

Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in Hb concentration from baseline to week 2.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	115		
Units: g/dL				
arithmetic mean (standard deviation)	0.04 (± 0.71)	-0.05 (± 0.69)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1239
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.1138
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.031
upper limit	0.259
Variability estimate	Standard error of the mean
Dispersion value	0.0737

Secondary: Change in Hb concentration from baseline to week 4

End point title	Change in Hb concentration from baseline to week 4

End point description:

Change in Hb concentration from baseline to week 4.

Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in Hb concentration from baseline to week 4.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	114		
Units: g/dL				
arithmetic mean (standard deviation)	0.01 (± 0.91)	-0.03 (± 0.68)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5233
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.0546
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.113
upper limit	0.223
Variability estimate	Standard error of the mean
Dispersion value	0.0854

Secondary: Change in Hb concentration from baseline to week 6.

End point title	Change in Hb concentration from baseline to week 6.
End point description:	
Change in Hb concentration from baseline to week 6. Analysis performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in Hb concentration from baseline to week 6.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	113		
Units: g/dL				
arithmetic mean (standard deviation)	-0.07 (± 1.11)	-0.06 (± 0.99)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8557
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.0069
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.204
upper limit	0.246
Variability estimate	Standard error of the mean
Dispersion value	0.1143

Secondary: Change in s-iron concentration from baseline to week 1

End point title	Change in s-iron concentration from baseline to week 1

End point description:

Change in s-iron concentration from baseline to week 1.

Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in s-iron concentration from baseline to week 1.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	112		
Units: micromol/L				
arithmetic mean (standard deviation)	1.45 (± 4.35)	0.75 (± 3.3)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1429
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.5793
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.197
upper limit	1.355
Variability estimate	Standard error of the mean
Dispersion value	0.3942

Secondary: Change in s-iron concentration from baseline to week 2

End point title	Change in s-iron concentration from baseline to week 2
End point description:	
Change in s-iron concentration from baseline to week 2. Analysis performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in s-iron concentration from baseline to week 2.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	115		
Units: micromol/L				
arithmetic mean (standard deviation)	1.07 (± 4.12)	0.64 (± 5.75)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5277
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.3761
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.797
upper limit	1.549
Variability estimate	Standard error of the mean
Dispersion value	0.5943

Secondary: Change in s-iron concentration from baseline to week 4

End point title	Change in s-iron concentration from baseline to week 4
End point description:	
Change in s-iron concentration from baseline to week 4. Analysis performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in s-iron concentration from baseline to week 4.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	114		
Units: micromol/L				
arithmetic mean (standard deviation)	0.81 (± 4.14)	1.08 (± 4.21)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.438
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.3576
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.265
upper limit	0.549
Variability estimate	Standard error of the mean
Dispersion value	0.4603

Secondary: Change in s-iron concentration from baseline to week 6

End point title	Change in s-iron concentration from baseline to week 6
End point description:	
Change in s-iron concentration from baseline to week 6. Analysis performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in s-iron concentration from baseline to week 6.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	113		
Units: micromol/L				
arithmetic mean (standard deviation)	0.82 (± 5.21)	0.76 (± 4.18)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9894
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.0066
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.965
upper limit	0.978
Variability estimate	Standard error of the mean
Dispersion value	0.4932

Secondary: Change in transferrin saturation (TSAT) concentration from baseline to week 1

End point title	Change in transferrin saturation (TSAT) concentration from baseline to week 1
End point description:	
Change in transferrin saturation (TSAT) concentration from baseline to week 1. Analysis performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in transferrin saturation (TSAT) concentration from baseline to week 1.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	111		
Units: percentage				
arithmetic mean (standard deviation)	2.8 (± 18.47)	9.16 (± 78.44)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.	
Comparison groups	Group B, iron sucrose v Group A, iron isomaltoside 1000
Number of subjects included in analysis	332
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.386
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-6.5236
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.376
upper limit	8.329
Variability estimate	Standard error of the mean
Dispersion value	7.4956

Secondary: Change in transferrin saturation (TSAT) concentration from baseline to week 2

End point title	Change in transferrin saturation (TSAT) concentration from baseline to week 2
End point description:	
Change in transferrin saturation (TSAT) concentration from baseline to week 2. Analysis performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in transferrin saturation (TSAT) concentration from baseline to week 2.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	115		
Units: percentage				
arithmetic mean (standard deviation)	2.45 (± 20.75)	1.44 (± 9.62)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.355
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1.1992
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.35
upper limit	3.748
Variability estimate	Standard error of the mean
Dispersion value	1.294

Secondary: Change in transferrin saturation (TSAT) concentration from baseline to week 4

End point title	Change in transferrin saturation (TSAT) concentration from baseline to week 4
End point description:	
Change in transferrin saturation (TSAT) concentration from baseline to week 4. Analysis performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in transferrin saturation (TSAT) concentration from baseline to week 4.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	114		
Units: percentage				
arithmetic mean (standard deviation)	1.8 (± 19.26)	2.85 (± 8.98)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3487
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.9972
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.09
upper limit	1.095
Variability estimate	Standard error of the mean
Dispersion value	1.0617

Secondary: Change in transferrin saturation (TSAT) concentration from baseline to week 6

End point title	Change in transferrin saturation (TSAT) concentration from baseline to week 6
End point description:	
Change in transferrin saturation (TSAT) concentration from baseline to week 6. Analysis performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in transferrin saturation (TSAT) concentration from baseline to week 6.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	113		
Units: percentage				
arithmetic mean (standard deviation)	2.29 (± 19.43)	2.42 (± 8.62)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9845
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.0207
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.118
upper limit	2.077
Variability estimate	Standard error of the mean
Dispersion value	1.0654

Secondary: Change in s-ferritin concentration from baseline to week 1

End point title	Change in s-ferritin concentration from baseline to week 1
End point description:	
Change in s-ferritin concentration from baseline to week 1. Analysis performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in s-ferritin concentration from baseline to week 1.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	113		
Units: microg/L				
arithmetic mean (standard deviation)	156.75 (± 148.91)	48.43 (± 75.36)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	107.8382
Confidence interval	
level	95 %
sides	2-sided
lower limit	87.987
upper limit	127.689
Variability estimate	Standard error of the mean
Dispersion value	10.0818

Secondary: Change in s-ferritin concentration from baseline to week 2

End point title	Change in s-ferritin concentration from baseline to week 2

End point description:

Change in s-ferritin concentration from baseline to week 2.

Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in s-ferritin concentration from baseline to week 2.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	115		
Units: microg/L				
arithmetic mean (standard deviation)	142.58 (± 187.82)	20.85 (± 94.84)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	123.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	96.449
upper limit	150.271
Variability estimate	Standard error of the mean
Dispersion value	13.6719

Secondary: Change in s-ferritin concentration from baseline to week 4

End point title	Change in s-ferritin concentration from baseline to week 4

End point description:

Change in s-ferritin concentration from baseline to week 4.

Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in s-ferritin concentration from baseline to week 4.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	114		
Units: microg/L				
arithmetic mean (standard deviation)	128.04 (± 157.75)	86.33 (± 126.79)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	49.3393
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.174
upper limit	80.505
Variability estimate	Standard error of the mean
Dispersion value	15.8282

Secondary: Change in s-ferritin concentration from baseline to week 6

End point title	Change in s-ferritin concentration from baseline to week 6

End point description:

Change in s-ferritin concentration from baseline to week 6.

Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in s-ferritin concentration from baseline to week 6.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	114		
Units: microg/L				
arithmetic mean (standard deviation)	136.2 (± 154.59)	156.3 (± 183.63)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4489
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-15.0585
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.196
upper limit	24.079
Variability estimate	Standard error of the mean
Dispersion value	19.8434

Secondary: Change in reticulocyte count from baseline to week 1

End point title	Change in reticulocyte count from baseline to week 1

End point description:

Change in reticulocyte count from baseline to week 1.

Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in reticulocyte count from baseline to week 1.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	108		
Units: percentage				
arithmetic mean (standard deviation)	0.12 (± 0.42)	-0.02 (± 0.38)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.154
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.066
upper limit	0.242
Variability estimate	Standard error of the mean
Dispersion value	0.0445

Secondary: Change in reticulocyte count from baseline to week 2

End point title	Change in reticulocyte count from baseline to week 2

End point description:

Change in reticulocyte count from baseline to week 2.

Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in reticulocyte count from baseline to week 2.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	111		
Units: percentage				
arithmetic mean (standard deviation)	0.05 (± 0.45)	0.02 (± 0.4)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3448
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.0439
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.047
upper limit	0.135
Variability estimate	Standard error of the mean
Dispersion value	0.0464

Secondary: Change in reticulocyte count from baseline to week 4

End point title	Change in reticulocyte count from baseline to week 4

End point description:

Change in reticulocyte count from baseline to week 4.

Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in reticulocyte count from baseline to week 4.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	110		
Units: percentage				
arithmetic mean (standard deviation)	0.05 (± 0.47)	0.03 (± 0.36)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5171
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.0302
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.061
upper limit	0.122
Variability estimate	Standard error of the mean
Dispersion value	0.0465

Secondary: Change in reticulocyte count from baseline to week 6

End point title	Change in reticulocyte count from baseline to week 6

End point description:

Change in reticulocyte count from baseline to week 6.

Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in reticulocyte count from baseline to week 6.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	109		
Units: percentage				
arithmetic mean (standard deviation)	0.06 (± 0.53)	0 (± 0.4)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1564
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.0727
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.028
upper limit	0.173
Variability estimate	Standard error of the mean
Dispersion value	0.0512

Secondary: Number of subjects in each randomisation group who discontinued study because of lack of response or intolerance of investigational drugs

End point title	Number of subjects in each randomisation group who discontinued study because of lack of response or intolerance of investigational drugs

End point description:

Number of subjects in each randomisation group who discontinued study because of lack of response or intolerance of investigational drugs.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

The endpoint covers the complete trial period.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	115		
Units: Number of subjects				
Discontinued due to intolerance/lack of response	1	0		
Discontinued due to other reasons	15	2		

Statistical analyses

Statistical analysis title	Superiority tested by Fisher Exact
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.9999
Method	Fisher exact

Secondary: Change in total quality of life (QoL) score (LASA: Energy level) from baseline to week 4

End point title	Change in total quality of life (QoL) score (LASA: Energy level) from baseline to week 4

End point description:

Change in total quality of life (QoL) score (LASA: Energy level) from baseline to week 4.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in total quality of life (QoL) score (LASA: Energy level) from baseline to week 4.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	111		
Units: QoL score				
arithmetic mean (standard deviation)	3.7 (± 19.64)	1.2 (± 16.74)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4653
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1.4173
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.402
upper limit	5.237
Variability estimate	Standard error of the mean
Dispersion value	1.9379

Secondary: Change in total quality of life (QoL) score (LASA: Energy level) from baseline to week 6

End point title	Change in total quality of life (QoL) score (LASA: Energy level) from baseline to week 6

End point description:

Change in total quality of life (QoL) score (LASA: Energy level) from baseline to week 6.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in total quality of life (QoL) score (LASA: Energy level) from baseline to week 6.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	113		
Units: QoL score				
arithmetic mean (standard deviation)	3.9 (± 18.91)	2.3 (± 17.54)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose

Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9539
Method	MRMM
Parameter estimate	Mean difference (final values)
Point estimate	0.1111
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.667
upper limit	3.889
Variability estimate	Standard error of the mean
Dispersion value	1.9182

Secondary: Change in total quality of life (QoL) score (LASA: Ability to do daily activities) from baseline to week 4

End point title	Change in total quality of life (QoL) score (LASA: Ability to do daily activities) from baseline to week 4

End point description:

Change in total quality of life (QoL) score (LASA: Ability to do daily activities) from baseline to week 4.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in total quality of life (QoL) score (LASA: Ability to do daily activities) from baseline to week 4.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	111		
Units: QoL score				
arithmetic mean (standard deviation)	2.2 (± 21.03)	-0.2 (± 14.25)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose

Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4086
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1.5719
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.168
upper limit	5.312
Variability estimate	Standard error of the mean
Dispersion value	1.8991

Secondary: Change in total quality of life (QoL) score (LASA: Ability to do daily activities) from baseline to week 6

End point title	Change in total quality of life (QoL) score (LASA: Ability to do daily activities) from baseline to week 6

End point description:

Change in total quality of life (QoL) score (LASA: Ability to do daily activities) from baseline to week 6.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in total quality of life (QoL) score (LASA: Ability to do daily activities) from baseline to week 6.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	113		
Units: QoL score				
arithmetic mean (standard deviation)	3.3 (± 19.6)	2.8 (± 17.91)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose

Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6734
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.8519
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.829
upper limit	3.125
Variability estimate	Standard error of the mean
Dispersion value	2.0186

Secondary: Change in total quality of life (QoL) score (LASA: Overall quality of life) from baseline to week 4

End point title	Change in total quality of life (QoL) score (LASA: Overall quality of life) from baseline to week 4

End point description:

Change in total quality of life (QoL) score (LASA: Overall quality of life) from baseline to week 4.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in total quality of life (QoL) score (LASA: Overall quality of life) from baseline to week 4.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	111		
Units: QoL score				
arithmetic mean (standard deviation)	1.7 (± 17.88)	-0.3 (± 15.63)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose

Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5711
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1.0565
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.614
upper limit	4.727
Variability estimate	Standard error of the mean
Dispersion value	1.8621

Secondary: Change in total quality of life (QoL) score (LASA: Overall quality of life) from baseline to week 6

End point title	Change in total quality of life (QoL) score (LASA: Overall quality of life) from baseline to week 6

End point description:

Change in total quality of life (QoL) score (LASA: Overall quality of life) from baseline to week 6.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in total quality of life (QoL) score (LASA: Overall quality of life) from baseline to week 6.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	113		
Units: QoL score				
arithmetic mean (standard deviation)	2 (± 18.56)	0.1 (± 15.65)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measures includes treatment, visit, treatment*visit interactions and stratum (s-ferritin (<100 vs. >=100 ng/mL)) ,country as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose

Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7964
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.4718
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.125
upper limit	4.069
Variability estimate	Standard error of the mean
Dispersion value	1.8264

Secondary: Change in restless legs syndrome (RLS) symptoms (Cambridge Hopkins-RLS questionnaire (CH-RLSq) score) from baseline to week 6 in subjects with RLS symptoms at baseline

End point title	Change in restless legs syndrome (RLS) symptoms (Cambridge Hopkins-RLS questionnaire (CH-RLSq) score) from baseline to week 6 in subjects with RLS symptoms at baseline

End point description:

Change in restless legs syndrome (RLS) symptoms (Cambridge Hopkins-RLS questionnaire (CH-RLSq) score) from baseline to week 6 in subjects with RLS symptoms at baseline.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in restless legs syndrome (RLS) symptoms (Cambridge Hopkins-RLS questionnaire (CH-RLSq) score) from baseline to week 6 in subjects with RLS symptoms at baseline.

End point values	Group A, iron isomaltoside 1000	Group B, iron sucrose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	40		
Units: RLS score				
arithmetic mean (standard deviation)	-0.7 (± 7.6)	-1.3 (± 5.37)		

Statistical analyses

Statistical analysis title	Superiority tested by ANCOVA

Statistical analysis description:

The ANCOVA mixed model includes treatment and stratum as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sucrose

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7267
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.4033
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.88
upper limit	2.686
Variability estimate	Standard error of the mean
Dispersion value	1.1507

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time a subject had signed the ICF and until he/she had completed the study, all AEs/SAEs were collected in the CRF. The SAEs occurring after study termination were re-ported if considered related to the study treatment.

Adverse event reporting additional description:

The principle investigator (PI) was responsible for ensuring that all AEs observed by PI or reported by the subject were properly collected and recorded in the subject's medical record as well as on the AE form.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Group A, iron isomaltoside 1000

Reporting group description:

All subjects received a cumulative dose of 500 mg iron isomaltoside 1000. Subjects in subgroup A1 were administered iron isomaltoside 1000 as a single undiluted IV bolus injection of 500 mg over approximately 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 week 2 and 4 as IV bolus injections over approximately 2 min.

Reporting group title	Group B, iron sucrose

Reporting group description:

All subjects received a cumulative dose of 500 mg iron sucrose. Subjects in group B were administered undiluted iron sucrose in split doses of 100 mg at baseline and 200 mg each at week 2 and 4.

Serious adverse events	Group A, iron isomaltoside 1000	Group B, iron sucrose	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 230 (9.57%)	6 / 114 (5.26%)	
number of deaths (all causes)	3	0	
number of deaths resulting from adverse events			
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Puncture site haemorrhage			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sudden death			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 230 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaesthetic complication			
subjects affected / exposed	0 / 230 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	2 / 230 (0.87%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 230 (1.30%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 230 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft occlusion			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arteriovenous fistula site infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected fistula			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 230 (0.43%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 230 (0.43%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Group A, iron isomaltoside 1000	Group B, iron sucrose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 230 (18.26%)	44 / 114 (38.60%)	
Investigations			
C-reactive protein increased			
subjects affected / exposed	6 / 230 (2.61%)	1 / 114 (0.88%)	
occurrences (all)	6	1	
Injury, poisoning and procedural complications			
Procedural hypotension			
subjects affected / exposed	5 / 230 (2.17%)	1 / 114 (0.88%)	
occurrences (all)	18	2	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 230 (3.04%)	4 / 114 (3.51%)	
occurrences (all)	7	5	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	5 / 230 (2.17%)	2 / 114 (1.75%)	
occurrences (all)	5	2	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	5 / 230 (2.17%)	0 / 114 (0.00%)	
occurrences (all)	6	0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	3 / 230 (1.30%)	3 / 114 (2.63%)	
occurrences (all)	4	3	
Nasopharyngitis			
subjects affected / exposed	6 / 230 (2.61%)	1 / 114 (0.88%)	
occurrences (all)	6	1	
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	5 / 230 (2.17%)	4 / 114 (3.51%)	
occurrences (all)	5	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2012	• Primary endpoint was changed from "change in Hb concentrations from baseline to week 6" to "proportion of subjects able to maintain Hb between 10 and 12.5 g/dl (both values included) at week 6" • In the secondary endpoint "change in Hb concentration from baseline to week 2 and 4", additional time point "week 6" was added • Study design was revised in terms of number of treatment groups and extension of enrolment period to 18 months, and study centre at Norway was removed from the list of participating countries • Text regarding iron isomaltoside 1000 was updated • Inclusion criteria pertaining to Hb, ESA treatment, and subjects not on IV iron and exclusion criterion 3 were modified to bring more clarity to text • Study flowchart was revised to clarify that height should be measured only at screening • The option of performing blood pregnancy test instead of UPT was added • Iron sucrose infusion time was changed to "according to SmPC" • Iron sucrose test dose administration was changed to "according to SmPC or local guidelines" • Statistical section was revised as per changes in the study endpoints (primary endpoint and first secondary endpoint) • The possibility of re-screening the screen-failure subjects once 2 weeks after the screening visit was added • Appendix 2 related to CH-RLSq was updated
10 July 2012	• Total study duration was increased to approximately 19 months, and study centres were rephrased as Europe, USA, and India • In inclusion criterion # 5, the target Hb range between "10 and 12.5 g/dL" was revised to "9.5 and 12.5 g/dL" • Additional text was included in sections: dosage and administration, prohibited medication, screen failure, and rescreening • Re-screening was allowed "up to 3 times" • The frequency of planned review by safety review committee was decreased from one meeting every 2 months to one meeting every 4 months for a feasible study conduct

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported