Clinical trial results:
A phase III, randomized, comparative, open-label study of intravenous iron isomaltoside 1000 (Monofer®) administered by infusions or repeated bolus injections in comparison with oral iron sulphate in subjects with non-dialysis dependent chronic kidney disease and with renal-related anaemia

Summary

EudraCT number	2009-016728-29
Trial protocol	SE DK GB IE DE PL AT
Global end of trial date	25 April 2014

Results information

Result version number	v2 (current)
This version publication date	30 March 2016
First version publication date	16 July 2015
Version creation reason	• Correction of full data set Some incorrect data was discovered during the review process.

Trial information

Trial identification

Sponsor protocol code	P-Monofer-CKD-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01102413
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, +45 59485935, trial@pharmacosmos.com
Scientific contact	Clinical trial disclosure desk, Pharmacosmos A/S, +45 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	25 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 April 2014
Global end of trial reached?	Yes
Global end of trial date	25 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that intravenous Iron Isomaltoside 1000 (Monofer®) is non-inferior to oral iron sulphate in reducing renal-related anaemia in NDD-CKD subjects, determined as ability to increase haemoglobin (Hb).

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	30 June 2010
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	India: 202
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Austria: 21
Country: Number of subjects enrolled	Denmark: 19
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Poland: 8
Worldwide total number of subjects	351
EEA total number of subjects	111

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)	244
From 65 to 84 years	93
85 years and over	14

Subject disposition

Recruitment

Recruitment details:

Subjects were screened in the period 30 June 2010 to 24 February 2014. The trial took place at 67 sites (hospitals or private dialysis clinics) in 3 continents: 17 in India, 10 in Germany, 7 in United Kingdom, 7 in Austria, 7 in Russia, 5 in Poland, 4 in Denmark, 3 in Romania, 3 in USA, 2 in Sweden, and 2 in Ireland.

Pre-assignment

Screening details:

Patients who were ≥18 years of age with estimated glomerular filtration rate (eGFR) between 15-59 mL/min/1.73 m2, Hb <11.0 g/dL, either or both of serum-ferritin <200 µg/L and TSAT < 20%, and had not received ESA treatment within 8 weeks prior to screening, were eligible to participate.

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:

The total IV iron needed for each subject in group A was calculated according to an adapted Ganzoni formula (target Hb was 13 g/dL (8.1 mmol/L) as the subjects were ESA naive): Cumulative iron dose (mg) = [body weight (kg) x (target Hb - actual Hb (g/dL)] x 2.4 + depot iron (set at 500 mg). Subjects treated with iron isomaltoside 1000 either received an IV infusion (group A1) of maximum 1000 mg iron isomaltoside 1000 as single doses over 15 minutes (full iron replacement was achieved by 1 or up to 2 doses at a weekly interval) or IV bolus injections (group A2) of 500 mg iron isomaltoside 1000 administered over 2 minutes once weekly until full replacement dose was achieved.

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:

The total IV iron needed for each subject in group A was calculated according to an adapted Ganzoni formula (target Hb was 13 g/dL (8.1 mmol/L) as the subjects were ESA naive): Cumulative iron dose (mg) = [body weight (kg) x (target Hb - actual Hb (g/dL)] x 2.4 + depot iron (set at 500 mg). Subjects treated with iron isomaltoside 1000 either received an IV infusion (group A1) of maximum 1000 mg iron isomaltoside 1000 as single doses over 15 minutes (full iron replacement was achieved by 1 or up to 2 doses at a weekly interval) or IV bolus injections (group A2) of 500 mg iron isomaltoside 1000 administered over 2 minutes once weekly until full replacement dose was achieved.
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 sulphate

Arm description:

Subjects receiving with oral iron sulphate were treated daily for 8 weeks with 200 mg given as 100 mg twice a day.

Arm type	Active comparator

Investigational medicinal product name	Iron sulphate
Investigational medicinal product code	ATC code: B03AA07
Other name	Ferro Duretter
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects receiving oral iron sulphate were treated daily for 8 weeks with 200 mg given as 100 mg twice a day.

Number of subjects in period 1	Group A, iron isomaltoside 1000	Group B, iron sulphate
Started	233	118
Completed	208	106
Not completed	25	12
Discontinued to take trial drug	-	1
Consent withdrawn by subject	9	3
Physician decision	1	-
Not eligeble, acute infection	-	1
Subject located to antoher city due new job.	1	-
Adverse event, non-fatal	3	5
Death	1	-
Lost to follow-up	5	2
Age limit </= 65, the subject is 74 years	1	-
Protocol deviation	3	-
Subject did not come due to social reasons.	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Group A, iron isomaltoside 1000
Reporting group description:	
The total IV iron needed for each subject in group A was calculated according to an adapted Ganzoni formula (target Hb was 13 g/dL (8.1 mmol/L) as the subjects were ESA naive): Cumulative iron dose (mg) = [body weight (kg) x (target Hb - actual Hb (g/dL)] x 2.4 + depot iron (set at 500 mg). Subjects treated with iron isomaltoside 1000 either received an IV infusion (group A1) of maximum 1000 mg iron isomaltoside 1000 as single doses over 15 minutes (full iron replacement was achieved by 1 or up to 2 doses at a weekly interval) or IV bolus injections (group A2) of 500 mg iron isomaltoside 1000 administered over 2 minutes once weekly until full replacement dose was achieved.	
Reporting group title	Group B, iron sulphate
Reporting group description:	
Subjects receiving with oral iron sulphate were treated daily for 8 weeks with 200 mg given as 100 mg twice a day.	

Reporting group values	Group A, iron isomaltoside 1000	Group B, iron sulphate	Total
Number of subjects	233	118	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	57.6	57.9	
standard deviation	± 15.5	± 16.3	-
Gender categorical Units: Subjects			
Female	141	54	195
Male	92	64	156

Subject analysis sets	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population (N=345) included all subjects who were randomised and received at least one dose of the trial drug.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) population (N=340) included all subjects who were randomised 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
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population (N=327) included all patients 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	Per protocol
Number of subjects	345	340	327
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	57.7	57.7	57.5
standard deviation	± 15.8	± 15.8	± 15.8
Gender categorical Units: Subjects			
Female	190	188	183
Male	155	152	144

End points

End points reporting groups

Reporting group title	Group A, iron isomaltoside 1000

Reporting group description:

The total IV iron needed for each subject in group A was calculated according to an adapted Ganzoni formula (target Hb was 13 g/dL (8.1 mmol/L) as the subjects were ESA naive): Cumulative iron dose (mg) = [body weight (kg) x (target Hb - actual Hb (g/dL)] x 2.4 + depot iron (set at 500 mg). Subjects treated with iron isomaltoside 1000 either received an IV infusion (group A1) of maximum 1000 mg iron isomaltoside 1000 as single doses over 15 minutes (full iron replacement was achieved by 1 or up to 2 doses at a weekly interval) or IV bolus injections (group A2) of 500 mg iron isomaltoside 1000 administered over 2 minutes once weekly until full replacement dose was achieved.

Reporting group title	Group B, iron sulphate

Reporting group description:

Subjects receiving with oral iron sulphate were treated daily for 8 weeks with 200 mg given as 100 mg twice a day.

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

Subject analysis set description:

The safety population (N=345) included all subjects who were randomised and received at least one dose of the trial drug.

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) population (N=340) included all subjects who were randomised 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
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population (N=327) included all patients in the FAS who did not have any major protocol deviation of clinical or statistical relevance.

Primary: Change in Hb concentration from baseline to week 4, FAS

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

End point description:

Change in Hb concentration from baseline to week 4.

Analysis performed on the FAS.

End point type	Primary

End point timeframe:

Change in Hb concentration from baseline to week 4.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	108		
Units: g/dL				
arithmetic mean (standard deviation)	0.57 (± 0.94)	0.35 (± 0.96)		

Statistical analyses

Statistical analysis title	Test for non-inferiority, MMRM

Statistical analysis description:

A mixed model for repeated measures (MMRM) was used to compare the average change in Hb concentration from baseline to week 4.
The number of subjects may differ from the analysis population if data is missing.
With a 2:1 randomisation, a two-sided significance level of 5%, and a non-inferiority margin of -0.5 g/dL, there was 80% power to demonstrate non-inferiority with 214 patients in group A and 107 patients in group B.

Comparison groups	Group B, iron sulphate v Group A, iron isomaltoside 1000
Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001 [2]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.2216
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.012
upper limit	0.431
Variability estimate	Standard error of the mean
Dispersion value	0.1064

Notes:

[1] - A mixed model for repeated measures (MMRM) was used to compare the average change in Hb concentration from baseline to week 4 with the inclusion of treatment, visit, treatment*visit interactions, country, and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 mL/min/1.73 m2 or between 46-59 mL/min/1.73 m2) as factors and baseline Hb as covariate. The treatment difference at week 4 was derived from the interaction between treatment and visit.
[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.

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

In case the 95 % CI lay entirely above 0, this was evidence of superiority in terms of statistical significance at the 5 % level. In that case, the p-value associated with a test of superiority was calculated and evaluated whether this was sufficiently small to reject the hypothesis of no difference.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0385
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.2216

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.012
upper limit	0.431
Variability estimate	Standard error of the mean
Dispersion value	0.1064

Primary: Change in Hb concentration from baseline to week 4, PP

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

End point description:

Change in Hb concentration from baseline to week 4.

The analysis is performed on the PP analysis set.

End point type	Primary

End point timeframe:

Change in Hb concentration from baseline to week 4.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	106		
Units: g/dL				
arithmetic mean (standard deviation)	0.56 (± 0.94)	0.34 (± 0.96)		

Statistical analyses

Statistical analysis title	Test for non-inferiority, MMRM

Statistical analysis description:

A mixed model for repeated measures (MMRM) was used to compare the average change in Hb concentration from baseline to week 4.
The number of subjects may differ from the analysis population if data is missing.
With a 2:1 randomisation, a two-sided significance level of 5%, and a non-inferiority margin of -0.5 g/dL, there was 80% power to demonstrate non-inferiority with 214 patients in group A and 107 patients in group B.

Comparison groups	Group B, iron sulphate v Group A, iron isomaltoside 1000
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.0001 [4]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.2176

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.003
upper limit	0.432
Variability estimate	Standard error of the mean
Dispersion value	0.109

Notes:

[3] - A mixed model for repeated measures (MMRM) was used to compare the average change in Hb concentration from baseline to week 4 with the inclusion of treatment, visit, treatment*visit interactions, country, and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 mL/min/1.73 m2 or between 46-59 mL/min/1.73 m2) as factors and baseline Hb as covariate. The treatment difference at week 4 was derived from the interaction between treatment and visit.
[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.

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

In case the 95 % CI lay entirely above 0, this was evidence of superiority in terms of statistical significance at the 5 % level. In that case, the p-value associated with a test of superiority was calculated and evaluated whether this was sufficiently small to reject the hypothesis of no difference.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0471 [6]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.2176
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.003
upper limit	0.432
Variability estimate	Standard error of the mean
Dispersion value	0.109

Notes:

[5] - A mixed model for repeated measures (MMRM) was used to compare the average change in Hb concentration from baseline to week 4 with the inclusion of treatment, visit, treatment*visit interactions, country, and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 mL/min/1.73 m2 or between 46-59 mL/min/1.73 m2) as factors and baseline Hb as covariate. The treatment difference at week 4 was derived from the interaction between treatment and visit.
[6] - 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: Number of subjects who had a change in Hb concentration ≥ 1.0 g/dL from baseline to week 2, 4, or 8

End point title	Number of subjects who had a change in Hb concentration ≥ 1.0 g/dL from baseline to week 2, 4, or 8

End point description:

The subjects had to have an increase in Hb ≥ 1.0 g/dL at either week 2,4, or week 8 in order to be a responder.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Number of subjects who had a change in Hb concentration ≥ 1.0 g/dL from baseline to week 2, 4, or 8.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	116		
Units: Proportion of subjects				
Responder	98	43		
Non-responder	124	73		

Statistical analyses

Statistical analysis title	Superiority test, logistic regression

Statistical analysis description:

The p-values is calculated with logistic regression with treatment and stratum as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1464
Method	Regression, Logistic

Secondary: Number of subjects who had a change in Hb concentration ≥ 2.0 g/dL from baseline to week 2, 4, or 8

End point title	Number of subjects who had a change in Hb concentration ≥ 2.0 g/dL from baseline to week 2, 4, or 8

End point description:

Number of subjects who had a change in Hb concentration ≥ 2.0 g/dL from baseline to week 2, 4, or 8.

The analysis was performed on FAS.

End point type	Secondary

End point timeframe:

Number of subjects who had a change in Hb concentration ≥ 2.0 g/dL from baseline to week 2, 4, or 8.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	116		
Units: Proportion of subjects				
Responder	33	12		
Non-responder	189	104		

Statistical analyses

Statistical analysis title	Superiority test, logistic regression
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.1792
Method	Regression, Logistic

Notes:

[7] - The p-value was calculated by Logistic Regression with treatment and stratum as factors and baseline values as covariates.

Secondary: Number of subjects who had Hb > 11 g/dL (6.80 mmol/L), serum (s)-ferritin (200-800 µg/L) and had achieved transferrin saturation (TSAT) (20-50 %) at week 2, 4, or 8

End point title	Number of subjects who had Hb > 11 g/dL (6.80 mmol/L), serum (s)-ferritin (200-800 µg/L) and had achieved transferrin saturation (TSAT) (20-50 %) at week 2, 4, or 8

End point description:

Number of subjects who had Hb > 11 g/dL (6.80 mmol/L), serum (s)-ferritin (200-800 µg/L) and had achieved transferrin saturation (TSAT) (20-50 %) at week 2, 4, or 8.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Number of subjects who had Hb > 11 g/dL (6.80 mmol/L), serum (s)-ferritin (200-800 µg/L) and had achieved transferrin saturation (TSAT) (20-50 %) at week 2, 4, or 8.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	116		
Units: Proportion of subjects				
Responder	40	6		
Non-responder	182	110		

Statistical analyses

Statistical analysis title	Superiority test, logistic regression

Statistical analysis description:

The p-value was calculated by logistic regression with treatment and stratum as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019
Method	Regression, Logistic

Secondary: Change in Hb from baseline to week 2

End point title	Change in Hb from baseline to week 2

End point description:

Change in Hb from baseline to week 2.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in Hb from baseline to week 2.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	110		
Units: g/dL				
arithmetic mean (standard deviation)	0.28 (± 0.67)	0.23 (± 0.78)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4902
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.0594

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.229
Variability estimate	Standard error of the mean
Dispersion value	0.0859

Secondary: Change in Hb from baseline to week 8

End point title	Change in Hb from baseline to week 8

End point description:

Change in Hb from baseline to week 8.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in Hb from baseline to week 8.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	112		
Units: g/dL				
arithmetic mean (standard deviation)	0.92 (± 1.19)	0.45 (± 1.04)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.445

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.199
upper limit	0.691
Variability estimate	Standard error of the mean
Dispersion value	0.1248

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

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

End point description:

Change in s-iron from baseline to week 1.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in s-iron from baseline to week 1.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	109		
Units: µmol/L				
arithmetic mean (standard deviation)	5.26 (± 14.46)	3.48 (± 7.06)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	3.5545
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.801
upper limit	5.308

Variability estimate	Standard error of the mean
Dispersion value	0.8896

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

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

End point description:

Change in s-iron from baseline to week 2.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in s-iron from baseline to week 2.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	110		
Units: µmol/L				
arithmetic mean (standard deviation)	3.03 (± 15.14)	2.67 (± 5.86)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0026
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	2.0305
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.716
upper limit	3.344
Variability estimate	Standard error of the mean
Dispersion value	0.6666

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

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

End point description:

Change in s-iron from baseline to week 4.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in s-iron from baseline to week 4.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	108		
Units: µmol/L				
arithmetic mean (standard deviation)	1.85 (± 14.9)	2.65 (± 5.33)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1439
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.8978
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.309
upper limit	2.104
Variability estimate	Standard error of the mean
Dispersion value	0.6119

Secondary: Change in s-iron from baseline to week 8

End point title	Change in s-iron from baseline to week 8

End point description:

Change in s-iron from baseline to week 8.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in s-iron from baseline to week 8.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	112		
Units: µmol/L				
arithmetic mean (standard deviation)	1.77 (± 15.04)	2.58 (± 5.48)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0914
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.9513
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.155
upper limit	2.057
Variability estimate	Standard error of the mean
Dispersion value	0.561

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

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

End point description:

Change in s-ferritin from baseline to week 1.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to week 1.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	109		
Units: µg/L				
arithmetic mean (standard deviation)	352.79 (± 184.12)	9.42 (± 33.3)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	321.4931
Confidence interval	
level	95 %
sides	2-sided
lower limit	270.348
upper limit	372.639
Variability estimate	Standard error of the mean
Dispersion value	25.4367

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

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

End point description:

Change in s-ferritin from baseline to week 2.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to week 2.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	110		
Units: µg/L				
arithmetic mean (standard deviation)	390.08 (± 212.67)	56.83 (± 434.25)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	334.9454
Confidence interval	
level	95 %
sides	2-sided
lower limit	251.812
upper limit	418.079
Variability estimate	Standard error of the mean
Dispersion value	42.0643

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

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

End point description:

Change in s-ferritin from baseline to week 4.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to week 4.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	108		
Units: µg/L				
arithmetic mean (standard deviation)	280.96 (± 175.51)	58.44 (± 337.5)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group B, iron sulphate v Group A, iron isomaltoside 1000
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	235.2231
Confidence interval	
level	95 %
sides	2-sided
lower limit	169.697
upper limit	300.749
Variability estimate	Standard error of the mean
Dispersion value	33.1761

Secondary: Change in s-ferritin from baseline to week 8

End point title	Change in s-ferritin from baseline to week 8

End point description:

Change in s-ferritin from baseline to week 8.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to week 8.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	112		
Units: µg/L				
arithmetic mean (standard deviation)	217.71 (± 160.34)	67.88 (± 250.21)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	155.6132
Confidence interval	
level	95 %
sides	2-sided
lower limit	104.764
upper limit	206.463
Variability estimate	Standard error of the mean
Dispersion value	25.7608

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

End point title	Change in transferrin saturation (TSAT) from baseline to week 1

End point description:

Change in transferrin saturation (TSAT) from baseline to week 1.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in transferrin saturation (TSAT) from baseline to week 1.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	109		
Units: Percentage				
arithmetic mean (standard deviation)	10.78 (± 29.72)	5.28 (± 10.2)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	8.3699
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.172
upper limit	11.568
Variability estimate	Standard error of the mean
Dispersion value	1.6246

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

End point title	Change in transferrin saturation (TSAT) from baseline to week 2

End point description:

Change in transferrin saturation (TSAT) from baseline to week 2.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in transferrin saturation (TSAT) from baseline to week 2.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	110		
Units: Percentage				
arithmetic mean (standard deviation)	7.86 (± 28.8)	4.56 (± 9.86)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	6.2022
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.862
upper limit	8.542
Variability estimate	Standard error of the mean
Dispersion value	1.1885

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

End point title	Change in transferrin saturation (TSAT) from baseline to week 4

End point description:

Change in transferrin saturation (TSAT) from baseline to week 4.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in transferrin saturation (TSAT) from baseline to week 4.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	108		
Units: Percentage				
arithmetic mean (standard deviation)	6.99 (± 29.4)	4.97 (± 8.87)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	4.7666
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.452
upper limit	7.082
Variability estimate	Standard error of the mean
Dispersion value	1.1759

Secondary: Change in transferrin saturation (TSAT) from baseline to week 8

End point title	Change in transferrin saturation (TSAT) from baseline to week 8

End point description:

Change in transferrin saturation (TSAT) from baseline to week 8.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in transferrin saturation (TSAT) from baseline to week 8.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	112		
Units: Percentage				
arithmetic mean (standard deviation)	6.37 (± 28.49)	6.11 (± 9.87)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0035
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	3.1969
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.063
upper limit	5.331
Variability estimate	Standard error of the mean
Dispersion value	1.0829

Secondary: Change in total iron binding capacity (TIBC) from baseline to week 1

End point title	Change in total iron binding capacity (TIBC) from baseline to week 1

End point description:

Change in total iron binding capacity (TIBC) from baseline to week 1.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in total iron binding capacity (TIBC) from baseline to week 1.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	109		
Units: µmol/L				
arithmetic mean (standard deviation)	-5.41 (± 8.18)	-0.5 (± 6.08)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-3.9216
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.43
upper limit	-2.413
Variability estimate	Standard error of the mean
Dispersion value	0.7652

Secondary: Change in total iron binding capacity (TIBC) from baseline to week 2

End point title	Change in total iron binding capacity (TIBC) from baseline to week 2

End point description:

Change in total iron binding capacity (TIBC) from baseline to week 2.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in total iron binding capacity (TIBC) from baseline to week 2.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	110		
Units: µmol/L				
arithmetic mean (standard deviation)	-8.17 (± 7.65)	-2.42 (± 9.82)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-5.1839
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.011
upper limit	-3.357
Variability estimate	Standard error of the mean
Dispersion value	0.9249

Secondary: Change in total iron binding capacity (TIBC) from baseline to week 4

End point title	Change in total iron binding capacity (TIBC) from baseline to week 4

End point description:

Change in total iron binding capacity (TIBC) from baseline to week 4.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in total iron binding capacity (TIBC) from baseline to week 4.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	108		
Units: µmol/L				
arithmetic mean (standard deviation)	-10.43 (± 11.94)	-2.63 (± 8.71)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-7.1556
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.987
upper limit	-5.324
Variability estimate	Standard error of the mean
Dispersion value	0.9303

Secondary: Change in total iron binding capacity (TIBC) from baseline to week 8

End point title	Change in total iron binding capacity (TIBC) from baseline to week 8

End point description:

Change in total iron binding capacity (TIBC) from baseline to week 8.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in total iron binding capacity (TIBC) from baseline to week 8.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	112		
Units: µmol/L				
arithmetic mean (standard deviation)	-10.74 (± 10.03)	-5.25 (± 8.82)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-4.7777
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.354
upper limit	-3.202
Variability estimate	Standard error of the mean
Dispersion value	0.7998

Secondary: Number of subjects who discontinued the study because of lack of response, need for blood transfusion, or intolerance of investigational drugs

End point title	Number of subjects who discontinued the study because of lack of response, need for blood transfusion, or intolerance of investigational drugs

End point description:

Number of subjects in each randomisation group who discontinued study because of lack of response, need for blood transfusion, or intolerance of investigational drugs.

The analysis was performed on the safety population.

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 sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	117		
Units: Number of subjects				
Discontinued due to intolerance/lack of response	2	1		
Discontinued due to other reasons	18	10		

Statistical analyses

Statistical analysis title	Superiority tested by Fisher Exact
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	345
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 sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	103		
Units: QoL score				
arithmetic mean (standard deviation)	5.79 (± 19.45)	7.67 (± 18.14)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM will include treatment, visit, treatment*visit interactions, country, stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6754
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.8106
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	4.62
Variability estimate	Standard error of the mean
Dispersion value	1.9327

Secondary: Change in total quality of life (QoL) score (LASA: Energy level) from baseline to week 8.

End point title	Change in total quality of life (QoL) score (LASA: Energy level) from baseline to week 8.

End point description:

Change in total quality of life (QoL) score (LASA: Energy level) from baseline to week 8.

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 8.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	108		
Units: QoL score				
arithmetic mean (standard deviation)	10.27 (± 20.83)	11.11 (± 20.44)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as

covariates.

Comparison groups	Group B, iron sulphate v Group A, iron isomaltoside 1000
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9625
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.09616
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.93
upper limit	4.12
Variability estimate	Standard error of the mean
Dispersion value	2.0424

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 sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	103		
Units: QoL score				
arithmetic mean (standard deviation)	4.42 (± 20.68)	4.02 (± 15.65)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

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

Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2788
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	2.0436
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	5.75
Variability estimate	Standard error of the mean
Dispersion value	1.8823

Secondary: Change in total quality of life (QoL) score (LASA: Ability to do daily activities) from baseline to week 8

End point title	Change in total quality of life (QoL) score (LASA: Ability to do daily activities) from baseline to week 8

End point description:

Change in total quality of life (QoL) score (LASA: Ability to do daily activities) from baseline to week 8.

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 8.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	108		
Units: QoL score				
arithmetic mean (standard deviation)	8.13 (± 20.52)	7.21 (± 19.84)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

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

Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3303
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	2.0155
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.06
upper limit	6.09
Variability estimate	Standard error of the mean
Dispersion value	2.0649

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 sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	103		
Units: QoL score				
arithmetic mean (standard deviation)	3.53 (± 19.84)	3.72 (± 16.27)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

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

Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3905
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1.5796
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.04
upper limit	5.2
Variability estimate	Standard error of the mean
Dispersion value	1.8359

Secondary: Change in total quality of life (QoL) score (LASA: Overall quality of life) from baseline to week 8

End point title	Change in total quality of life (QoL) score (LASA: Overall quality of life) from baseline to week 8

End point description:

Change in total quality of life (QoL) score (LASA: Overall quality of life) from baseline to week 8.

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 8.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	108		
Units: QoL score				
arithmetic mean (standard deviation)	7.29 (± 20.51)	6.47 (± 20.07)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline value as covariates.

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

Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4723
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1.4573
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.53
upper limit	5.45
Variability estimate	Standard error of the mean
Dispersion value	2.0236

Secondary: Change in estimated glomerular filtration rate (eGFR) from baseline to week 8

End point title	Change in estimated glomerular filtration rate (eGFR) from baseline to week 8

End point description:

Change in estimated glomerular filtration rate (eGFR) from baseline to week 8.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in estimated glomerular filtration rate (eGFR) from baseline to week 8.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	112		
Units: mL/min/1.73 m2				
arithmetic mean (standard deviation)	-0.19 (± 7.78)	-0.91 (± 6.53)		

Statistical analyses

Statistical analysis title	Superiority tested by ANCOVA

Statistical analysis description:

The ANCOVA model included treatment and stratum (past treatment with parenteral iron (Yes/No) and current eGFR between 15-45 ml/min or between 46-59 ml/min) as factors and baseline values as covariates.

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

Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4493
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.6548
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	2.36
Variability estimate	Standard error of the mean
Dispersion value	0.8645

Secondary: Change in restless legs syndrome (RLS) symptoms (Cambridge-Hopkins RLS questionnaire (CH-RLSq) score) from baseline to week 8 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 8 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 8 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 8 in subjects with RLS symptoms at baseline.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: RLS score				
arithmetic mean (standard deviation)	-7 (± 15.87)	-6.33 (± 13.65)		

Statistical analyses

Statistical analysis title	Superiority tested by ANCOVA

Statistical analysis description:

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

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

Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5957
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.4739
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.936
upper limit	26.884
Variability estimate	Standard error of the mean
Dispersion value	1.9998

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 trial, all AEs/SAEs were collected in the CRF.

Adverse event reporting additional description:

All AEs classified as serious and/or related to the study drug were followed by the principle investigator (PI) until the subject had recovered, recovered with sequelae, or died, and until all queries related to the AEs had been resolved. All other AEs were followed by the PI until the subject had recovered or until EOS whichever came first.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Group A, iron isomaltoside 1000

Reporting group description:

The total IV iron needed for each subject in group A was calculated according to an adapted Ganzoni formula (target Hb was 13 g/dL (8.1 mmol/L) as the subjects were ESA naive): Cumulative iron dose (mg) = [body weight (kg) x (target Hb - actual Hb (g/dL)] x 2.4 + depot iron (set at 500 mg). Subjects treated with iron isomaltoside 1000 either received an IV infusion (group A1) of maximum 1000 mg iron isomaltoside 1000 as single doses over 15 minutes (full iron replacement was achieved by 1 or up to 2 doses at a weekly interval) or IV bolus injections (group A2) of 500 mg iron isomaltoside 1000 administered over 2 minutes once weekly until full replacement dose was achieved.

Reporting group title	Group B, oral iron sulphate

Reporting group description:

Subjects receiving with oral iron sulphate were treated daily for 8 weeks with 200 mg given as 100 mg twice a day.

Serious adverse events	Group A, iron isomaltoside 1000	Group B, oral iron sulphate	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 228 (5.26%)	10 / 117 (8.55%)	
number of deaths (all causes)	3	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 228 (0.44%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 228 (0.44%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	0 / 228 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	0 / 228 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 228 (0.44%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 228 (0.44%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiorenal syndrome			
subjects affected / exposed	0 / 228 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 228 (0.44%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 117 (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			

Carotid artery stenosis			
subjects affected / exposed	1 / 228 (0.44%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 228 (0.44%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 228 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 228 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 228 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 228 (0.88%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 228 (0.44%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	0 / 228 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 228 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 228 (0.00%)	1 / 117 (0.85%)	
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	1 / 228 (0.44%)	0 / 117 (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			
Renal failure acute			
subjects affected / exposed	1 / 228 (0.44%)	0 / 117 (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			
Plasmodium falciparum infection			
subjects affected / exposed	1 / 228 (0.44%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 228 (0.88%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia staphylococcal			

subjects affected / exposed	0 / 228 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 228 (0.44%)	0 / 117 (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, oral iron sulphate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 228 (18.42%)	22 / 117 (18.80%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 228 (2.63%)	2 / 117 (1.71%)	
occurrences (all)	6	2	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	5 / 228 (2.19%)	2 / 117 (1.71%)	
occurrences (all)	5	2	
Pyrexia			
subjects affected / exposed	7 / 228 (3.07%)	4 / 117 (3.42%)	
occurrences (all)	7	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 228 (2.63%)	4 / 117 (3.42%)	
occurrences (all)	6	4	
Faeces discoloured			
subjects affected / exposed	0 / 228 (0.00%)	5 / 117 (4.27%)	
occurrences (all)	0	5	
Vomiting			
subjects affected / exposed	6 / 228 (2.63%)	1 / 117 (0.85%)	
occurrences (all)	7	1	
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	5 / 228 (2.19%) 5	0 / 117 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 228 (3.07%) 9	4 / 117 (3.42%) 5	
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	6 / 228 (2.63%) 7	0 / 117 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2010	• The replacement dose was modified to 750 mg iron isomaltoside 1000 for subjects with body weight between 35-45 kg and 500 mg iron isomaltoside 1000 for < 35 kg body weight • Laboratory assessment of s-calcium was added to obtain a complete serum chemistry • It was clarified that the UPT will be done only at screening • Packaging of iron isomaltoside 1000 was changed from 10 mL (1000 mg iron) am-poules to 5 mL (500 mg iron) vials • Analysis of phosphate as part of safety lab after 25, 50, and 100 subjects had been ex-posed to iron isomaltoside 1000 was added to monitor changes in phosphate levels
28 September 2011	• Subjects with body weight < 30 kg were excluded from the study for safety reasons • In the secondary endpoints, target limits for Hb, s-ferritin, and TSAT were removed on request from investigators, as these limits were too high • Text regarding the number of study centres was revised from "4 countries (UK, Denmark, Sweden, and India)" to "several countries in the European Union and India" • Levels of s-ferritin in the inclusion criteria were modified from s-ferritin < 100 µg/L to s-ferritin < 200 µg/L • Text describing non-serious AEs, ADRs, and SUSARs were added for clarity • Text regarding "3 months follow-up for pregnancy and study drug related SAEs" after EOS was removed
18 March 2013	• Primary endpoint of change in Hb concentration from baseline was changed from week 8 to week 4. • In the secondary endpoints, it was clarified that the responder can fulfil the criteria at any time point instead of all time points • A secondary endpoint of the number of subjects with a change in Hb ≥ 2.0 g/dL at different time points was added, in alignment with previous studies • The number of AEs of special interest (i.e. hypersensitivity reactions or hypotension at pre-specified time points in relation to administration of study drug) was added as a secondary endpoint • Secondary endpoint of change in Hb concentration was changed from week 4 to week 8 in order to align with the change in primary endpoint • Exclusion criteria 5 was modified to clarify that if the subject did not have an impaired liver function then there was no need to exclude the subject from the study. • Exclusion criteria no. 6 and 20 were removed as there was no increased risk for subjects infected with human immunodeficiency virus or hepatitis virus in participating in the study and it is not a contraindication in the SmPC of the study drug • To allow addition of new centres in countries other than Europe and India, the text describing the participating countries was generalised • Window periods for recording vital signs were increased from 0-5 to 0-10 min, and approximate time points were added for 5 min and 30 min after injection to allow a more flexible procedure • The word "approximately" was added to the administration time in order to make the drug administration more flexible for the centre personal • The provision for re-screening was added • The pregnancy reporting procedure was updated as there is no safety issue for women of which the spouse has been enrolled in the study • Appendix 2 related to CH-RLSq was updated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported