Clinical trial results:
A phase III, randomized, open-label study of intravenous iron isomaltoside 1000 (Monofer®) as mono therapy (without erythropoeisis stimulating agents) in comparison with oral iron sulfate in subjects with non-myeloid malignancies associated with Chemotherapy induced anaemia (CIA)

Summary

EudraCT number	2009-016727-53
Trial protocol	DK GB SE DE ES
Global end of trial date	23 April 2014

Results information

Result version number	v2 (current)
This version publication date	06 April 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-CIA-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01145638
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	23 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 April 2014
Global end of trial reached?	Yes
Global end of trial date	23 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 the ability to increase haemoglobin (Hb) in subjects with chemotherapy induced anemia and either absolute or functional iron deficiency.

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	19 October 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	Russian Federation: 47
Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	India: 205
Country: Number of subjects enrolled	Poland: 56
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Germany: 10
Worldwide total number of subjects	350
EEA total number of subjects	80

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	288
From 65 to 84 years	61
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects were screened in the period 19 October 2010 to 30 October 2013. The trial took place at 47 sites (hospitals or private cancer clinics) in 3 continents: 18 in India, 9 in Russia, 7 in Poland, 4 in Germany, 3 in USA, 2 in Sweden and Spain, and 1 in Denmark and UK.

Pre-assignment

Screening details:

Patients who were ≥18 years of age, diagnosed with non-myeloid malignancies receiving chemotherapy at least 1 day prior to screening and who were going to receive at least 2 more chemotherapy cycles, Hb <12.0 g/dL, TSAT <50%, ferritin <800 µg/L, and with an eastern cooperative oncology group performance status of 0-2 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:

Subjects treated with iron isomaltoside 1000 were randomised to either an IV infusion (group A1) of maximum 1000 mg (the maximum dose per infusion was 1000 mg for subjects with a weight >45 kg, 750 mg for subjects with a weight between 35 and 45 kg, and 500 mg for subjects with a weight <35 kg) iron isomaltoside 1000 as single doses over approximately 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 approximately 2 minutes once weekly until full replacement dose was achieved (a total of 1-4 doses at a weekly interval).

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:

Subjects treated with iron isomaltoside 1000 were randomised to either an IV infusion (group A1) of maximum 1000 mg (the maximum dose per infusion was 1000 mg for subjects with a weight >45 kg, 750 mg for subjects with a weight between 35 and 45 kg, and 500 mg for subjects with a weight <35 kg) iron isomaltoside 1000 as single doses over approximately 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 approximately 2 minutes once weekly until full replacement dose was achieved (a total of 1-4 doses at a weekly interval).
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 oral iron sulphate were treated daily for 12 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 12 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	231	119
Completed	141	62
Not completed	90	57
Adverse event, serious fatal	7	8
No reason given (incorrectly randomised)	1	-
Physician decision	5	5
Subject decission to discontinue	1	-
SAE discharged to nursing home	-	1
Randomisation failure	-	1
Progressive disease, brain mts	-	1
ICF withdrawl due to worsening of cancer	1	-
Not ready for furhter allopathy treatment	1	-
Consent withdrawn by subject	34	18
Adverse event, non-fatal	16	11
Death	3	-
Lost to follow-up	12	10
Finished the study earlier due to traveling	1	-
Protocol deviation	8	2

Baseline characteristics

Reporting groups	
Reporting group title	Group A, iron isomaltoside 1000
Reporting group description:	
Subjects treated with iron isomaltoside 1000 were randomised to either an IV infusion (group A1) of maximum 1000 mg (the maximum dose per infusion was 1000 mg for subjects with a weight >45 kg, 750 mg for subjects with a weight between 35 and 45 kg, and 500 mg for subjects with a weight <35 kg) iron isomaltoside 1000 as single doses over approximately 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 approximately 2 minutes once weekly until full replacement dose was achieved (a total of 1-4 doses at a weekly interval).	
Reporting group title	Group B, iron sulphate
Reporting group description:	
Subjects receiving oral iron sulphate were treated daily for 12 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	231	119	350
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	54.83	53.92	
standard deviation	± 11.66	± 11.05	-
Gender categorical Units: Subjects			
Female	151	90	241
Male	80	29	109

Subject analysis sets	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population (N=341) 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 (N=337) 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 analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol population (N=315) 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	Per protocol analysis set
Number of subjects	341	337	315
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	54.6	54.7	54.3
standard deviation	± 11.5	± 11.5	± 11.2
Gender categorical Units: Subjects			
Female	234	232	218
Male	107	105	97

End points

End points reporting groups

Reporting group title	Group A, iron isomaltoside 1000

Reporting group description:

Subjects treated with iron isomaltoside 1000 were randomised to either an IV infusion (group A1) of maximum 1000 mg (the maximum dose per infusion was 1000 mg for subjects with a weight >45 kg, 750 mg for subjects with a weight between 35 and 45 kg, and 500 mg for subjects with a weight <35 kg) iron isomaltoside 1000 as single doses over approximately 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 approximately 2 minutes once weekly until full replacement dose was achieved (a total of 1-4 doses at a weekly interval).

Reporting group title	Group B, iron sulphate

Reporting group description:

Subjects receiving oral iron sulphate were treated daily for 12 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=341) 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 (N=337) 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 analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol population (N=315) included all subjects 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:

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	192	99		
Units: g/dL				
arithmetic mean (standard deviation)	0.48 (± 1.2)	0.44 (± 1.24)		

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.
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 subjects in group A and 107 subjects in group B.

Comparison groups	Group B, iron sulphate v Group A, iron isomaltoside 1000
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.0002 [2]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.0161
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.261
upper limit	0.293
Variability estimate	Standard error of the mean
Dispersion value	0.1406

Notes:

[1] - Treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country were included as factors and baseline Hb were included as covariate. The treatment difference at week 4 was derived from the interaction between treatment and visit.
The primary analysis was to assess non-inferiority and the non-inferiority margin was set as -0.5 g/dL.

[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:

From the primary analysis model, the p-value for the test of superiority of group A (iron isomaltoside 1000 group) versus group B (iron sulphate group) was derived.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9092
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.0161
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.261
upper limit	0.293
Variability estimate	Standard error of the mean
Dispersion value	0.1406

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: 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	184	89		
Units: g/dL				
arithmetic mean (standard deviation)	0.44 (± 1.18)	0.43 (± 1.19)		

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 subjects in group A and 107 subjects in group B.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.0006 [4]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.0071
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.291
upper limit	0.276
Variability estimate	Standard error of the mean
Dispersion value	0.1436

Notes:

[3] - Treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country were included as factors and baseline Hb were included as covariate. The treatment difference at week 4 was derived from the interaction between treatment and visit.
The primary analysis was to assess non-inferiority and the non-inferiority margin was set as -0.5 g/dL.

[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	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9609
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.0071
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.291
upper limit	0.276
Variability estimate	Standard error of the mean
Dispersion value	0.1436

Secondary: Proportion of subjects who achieved target limits of Hb (men 13-18 g/dL, women 12-16 g/dL) and had change in Hb concentration ≥ 1.0 g/dL at week 2, 4, 8, or 12

End point title	Proportion of subjects who achieved target limits of Hb (men 13-18 g/dL, women 12-16 g/dL) and had change in Hb concentration ≥ 1.0 g/dL at week 2, 4, 8, or 12

End point description:

The subjects needed to fulfill 2 criteria in order to be a responder:
1) achieved target limits of Hb (men 13-18 g/dL, women 12-16 g/dL)
2) have had a change in Hb concentration ≥ 1.0 g/dL at week 2, 4, 8, or 12

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Proportion of subjects who achieved target limits of Hb (men 13-18 g/dL, women 12-16 g/dL) and had change in Hb concentration ≥ 1.0 g/dL at week 2, 4, 8, or 12.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214	105		
Units: Fraction of patients				
Responder	54	24		
Non-responder	160	81		

Statistical analyses

Statistical analysis title	Test for superiority, logistic regression

Statistical analysis description:

The p-value is calculated by logistic regression with treatment and platinum based chemotherapy (Yes/No) as factors and baseline values as covariates using PROC LOGISTIC Procedure.

Comparison groups	Group B, iron sulphate v Group A, iron isomaltoside 1000
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7772
Method	Regression, Logistic

Secondary: Proportion of subjects who had a change in Hb concentration ≥ 2.0 g/dL at week 2 or 4

End point title	Proportion of subjects who had a change in Hb concentration ≥ 2.0 g/dL at week 2 or 4

End point description:

The subjects had to have an increase in Hb ≥ 2.0 g/dL at either week 2 or week 4 in order to be a responder.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Proportion of subjects who had a change in Hb concentration ≥ 2.0 g/dL at week 2 or 4.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	105		
Units: Fraction of patients				
Responder	20	16		
Non-responder	193	89		

Statistical analyses

Statistical analysis title	Superiority test, logistic regression

Statistical analysis description:

The p-value is calculated by logistic regression with treatment and platinum based chemotherapy (Yes/No) 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	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1193
Method	Regression, Logistic

Secondary: Proportion of subjects who had a change in Hb concentration ≥ 2.0 g/dL at week 2, 4, 8, or 12

End point title	Proportion of subjects who had a change in Hb concentration ≥ 2.0 g/dL at week 2, 4, 8, or 12

End point description:

The subjects had to have an increase in Hb ≥ 2.0 g/dL at either week 2, 4, 8 or 12 in order to be a responder.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Proportion of subjects who had a change in Hb concentration ≥ 2.0 g/dL at week 2, 4, 8, or 12.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214	105		
Units: Proportion of subjects				
Responder	61	29		
Non-responder	153	76		

Statistical analyses

Statistical analysis title	Superiority tested by logistic regression

Statistical analysis description:

The p-value is calculated by Logistic Regression with treatment and platinum based chemotherapy (Yes/No) 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	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8372
Method	Regression, Logistic

Secondary: Number of subjects receiving transfusions

End point title	Number of subjects receiving transfusions

End point description:

Number of subjects receiving transfusions.

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 sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	112		
Units: Proportion of subjects				
Yes, recieved transfusion	17	6		
No, did not recieve transfusion	208	106		

Statistical analyses

Statistical analysis title	Superiority tested by chi-squared

Statistical analysis description:

The p-value was calculated by using chi-squared.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4509
Method	Chi-squared

Secondary: Change in Hb from baseline to week 1

End point title	Change in Hb from baseline to week 1

End point description:

Change in Hb from baseline to week 1.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in Hb 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	215	110		
Units: g/dL				
arithmetic mean (standard deviation)	0.11 (± 0.89)	-0.08 (± 1.13)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0799
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.2006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.024
upper limit	0.425
Variability estimate	Standard error of the mean
Dispersion value	0.1139

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	100		
Units: g/dL				
arithmetic mean (standard deviation)	0.33 (± 1.03)	0.17 (± 1.16)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
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
P-value	= 0.2448
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.1502
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.104
upper limit	0.404
Variability estimate	Standard error of the mean
Dispersion value	0.1287

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	181	84		
Units: g/dL				
arithmetic mean (standard deviation)	0.78 (± 1.52)	0.82 (± 1.44)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.881
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.0268
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.326
upper limit	0.379
Variability estimate	Standard error of the mean
Dispersion value	0.1788

Secondary: Change in Hb from baseline to week 12

End point title	Change in Hb from baseline to week 12
End point description:	
Change in Hb from baseline to week 12. The analysis was performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in Hb from baseline to week 12.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	81		
Units: g/dL				
arithmetic mean (standard deviation)	1.24 (± 1.57)	1.11 (± 1.73)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5786
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.1152
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.294
upper limit	0.524
Variability estimate	Standard error of the mean
Dispersion value	0.2071

Secondary: Change in Hb from baseline to week 24

End point title	Change in Hb from baseline to week 24
End point description:	
Change in Hb from baseline to week 24. The analysis was performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in Hb from baseline to week 24.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	72		
Units: g/dL				
arithmetic mean (standard deviation)	1.6 (± 1.95)	1.78 (± 2.16)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8495
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.0526
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.599
upper limit	0.494
Variability estimate	Standard error of the mean
Dispersion value	0.2766

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	216	109		
Units: µmol/L				
arithmetic mean (standard deviation)	-3.45 (± 8.16)	-0.71 (± 7.55)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-2.5652
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.252
upper limit	-0.878
Variability estimate	Standard error of the mean
Dispersion value	0.856

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	210	100		
Units: µmol/L				
arithmetic mean (standard deviation)	-5.65 (± 8.6)	-2.13 (± 8.73)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
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
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-3.7922
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.599
upper limit	-1.985
Variability estimate	Standard error of the mean
Dispersion value	0.9164

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	194	98		
Units: µmol/L				
arithmetic mean (standard deviation)	-7.18 (± 10.41)	-2.75 (± 10.01)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-4.6663
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.901
upper limit	-2.432
Variability estimate	Standard error of the mean
Dispersion value	1.1327

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	182	84		
Units: µmol/L				
arithmetic mean (standard deviation)	-6.24 (± 11.04)	-3.09 (± 13.01)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0278
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-3.1772
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.002
upper limit	-0.352
Variability estimate	Standard error of the mean
Dispersion value	0.0278

Secondary: Change in total iron binding capacity (TIBC) from baseline to week 12

End point title	Change in total iron binding capacity (TIBC) from baseline to week 12

End point description:

Change in total iron binding capacity (TIBC) from baseline to week 12.

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 12.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	81		
Units: µmol/L				
arithmetic mean (standard deviation)	-4.04 (± 11.86)	-2.68 (± 11.63)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/ No), and country as factors and baseline value as covariate.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1662
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.8274
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.421
upper limit	0.766
Variability estimate	Standard error of the mean
Dispersion value	1.3151

Secondary: Change in total iron binding capacity (TIBC) from baseline to week 24

End point title	Change in total iron binding capacity (TIBC) from baseline to week 24

End point description:

Change in total iron binding capacity (TIBC) from baseline to week 24.

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 24.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	72		
Units: µmol/L				
arithmetic mean (standard deviation)	-3.23 (± 13.03)	0.79 (± 11.57)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0396
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-3.2405
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.325
upper limit	-0.156
Variability estimate	Standard error of the mean
Dispersion value	1.5614

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	216	109		
Units: µmol/L				
arithmetic mean (standard deviation)	4.99 (± 17.36)	-0.09 (± 13.08)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	3.3255
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.708
upper limit	5.943
Variability estimate	Standard error of the mean
Dispersion value	1.33

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.	
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	210	100		
Units: µmol/L				
arithmetic mean (standard deviation)	3.67 (± 13.9)	1.55 (± 16.29)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
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
P-value	= 0.9993
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.0014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.91
upper limit	2.908
Variability estimate	Standard error of the mean
Dispersion value	1.474

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	194	98		
Units: µmol/L				
arithmetic mean (standard deviation)	2.7 (± 14.5)	1.11 (± 12.47)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
Comparison groups	Group B, iron sulphate v Group A, iron isomaltoside 1000
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9473
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.0801
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.463
upper limit	2.303
Variability estimate	Standard error of the mean
Dispersion value	1.2092

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	182	84		
Units: µmol/L				
arithmetic mean (standard deviation)	1.03 (± 13.74)	0.97 (± 13.1)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3829
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.0612
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.457
upper limit	1.335
Variability estimate	Standard error of the mean
Dispersion value	1.2126

Secondary: Change in s-iron from baseline to week 12

End point title	Change in s-iron from baseline to week 12
End point description:	
Change in s-iron from baseline to week 12. The analysis was performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in s-iron from baseline to week 12.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	81		
Units: µmol/L				
arithmetic mean (standard deviation)	0.89 (± 13.59)	1.49 (± 13.89)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1239
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-2.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.676
upper limit	0.57
Variability estimate	Standard error of the mean
Dispersion value	1.3251

Secondary: Change in s-iron from baseline to week 24

End point title	Change in s-iron from baseline to week 24
End point description:	
Change in s-iron from baseline to week 24. The analysis was performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in s-iron from baseline to week 24.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	72		
Units: µmol/L				
arithmetic mean (standard deviation)	-0.36 (± 12.92)	-2.2 (± 15.36)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7693
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.3722
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.879
upper limit	2.135
Variability estimate	Standard error of the mean
Dispersion value	1.2656

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	216	109		
Units: µg/L				
arithmetic mean (standard deviation)	455.71 (± 338.1)	20.9 (± 190.82)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/ No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	434.9819
Confidence interval	
level	95 %
sides	2-sided
lower limit	377.818
upper limit	492.146
Variability estimate	Standard error of the mean
Dispersion value	29.0261

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	100		
Units: µg/L				
arithmetic mean (standard deviation)	507.35 (± 597.19)	29.27 (± 257.39)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/ No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	477.6825
Confidence interval	
level	95 %
sides	2-sided
lower limit	373.581
upper limit	581.785
Variability estimate	Standard error of the mean
Dispersion value	51.1129

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	193	98		
Units: µg/L				
arithmetic mean (standard deviation)	390.06 (± 342.32)	65.54 (± 268.57)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/ No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	324.0235
Confidence interval	
level	95 %
sides	2-sided
lower limit	253.896
upper limit	394.151
Variability estimate	Standard error of the mean
Dispersion value	35.6293

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	182	84		
Units: µg/L				
arithmetic mean (standard deviation)	265.61 (± 310.9)	28.5 (± 186.71)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/ No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	234.8969
Confidence interval	
level	95 %
sides	2-sided
lower limit	174.5
upper limit	295.294
Variability estimate	Standard error of the mean
Dispersion value	30.6672

Secondary: Change in s-ferritin from baseline to week 12

End point title	Change in s-ferritin from baseline to week 12
End point description:	
Change in s-ferritin from baseline to week 12. The analysis was performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in s-ferritin from baseline to week 12.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	81		
Units: µg/L				
arithmetic mean (standard deviation)	174.63 (± 287.96)	4.38 (± 233.25)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/ No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	179.2712
Confidence interval	
level	95 %
sides	2-sided
lower limit	112.44
upper limit	246.102
Variability estimate	Standard error of the mean
Dispersion value	33.8524

Secondary: Change in s-ferritin from baseline to week 24

End point title	Change in s-ferritin from baseline to week 24
End point description:	
Change in s-ferritin from baseline to week 24. The analysis was performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in s-ferritin from baseline to week 24.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	72		
Units: µg/L				
arithmetic mean (standard deviation)	219.88 (± 635.63)	1.93 (± 315.61)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	224.8656
Confidence interval	
level	95 %
sides	2-sided
lower limit	102.9
upper limit	346.831
Variability estimate	Standard error of the mean
Dispersion value	61.9284

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	216	109		
Units: percentage				
arithmetic mean (standard deviation)	8.78 (± 26.25)	0.16 (± 19.91)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0025
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	6.1406
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.179
upper limit	10.102
Variability estimate	Standard error of the mean
Dispersion value	2.0124

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	210	100		
Units: percentage				
arithmetic mean (standard deviation)	7.51 (± 23.19)	2.98 (± 27.71)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
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
P-value	= 0.4567
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1.7931
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.951
upper limit	6.537
Variability estimate	Standard error of the mean
Dispersion value	2.4038

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	194	98		
Units: percentage				
arithmetic mean (standard deviation)	6.43 (± 24.39)	2.47 (± 20.71)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4655
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1.4872
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.522
upper limit	5.496
Variability estimate	Standard error of the mean
Dispersion value	2.034

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	182	84		
Units: percentage				
arithmetic mean (standard deviation)	3.92 (± 22.95)	2.45 (± 21.04)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9401
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.1555
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.235
upper limit	3.924
Variability estimate	Standard error of the mean
Dispersion value	2.0659

Secondary: Change in transferrin saturation (TSAT) from baseline to week 12

End point title	Change in transferrin saturation (TSAT) from baseline to week 12
End point description:	
Change in transferrin saturation (TSAT) from baseline to week 12. The analysis was performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in transferrin saturation (TSAT) from baseline to week 12.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	81		
Units: percentage				
arithmetic mean (standard deviation)	2.76 (± 21.7)	2.17 (± 21.85)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4541
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.5555
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.651
upper limit	2.54
Variability estimate	Standard error of the mean
Dispersion value	2.0722

Secondary: Change in transferrin saturation (TSAT) from baseline to week 24

End point title	Change in transferrin saturation (TSAT) from baseline to week 24
End point description:	
Change in transferrin saturation (TSAT) from baseline to week 24. The analysis was performed on the FAS.	
End point type	Secondary
End point timeframe:	
Change in transferrin saturation (TSAT) from baseline to week 24.	

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	72		
Units: percentage				
arithmetic mean (standard deviation)	0.05 (± 21.39)	-4.1 (± 25.48)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM
Statistical analysis description:	
The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7359
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.7721
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.752
upper limit	5.296
Variability estimate	Standard error of the mean
Dispersion value	2.2839

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 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	89	50		
Units: Number of subjects				
Discontinued due to intolerance/lack of response	2	10		
Discontinued due to other reasons	87	40		

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	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Fisher exact

Secondary: Change in quality of life (QoL) from baseline to week 4

End point title	Change in quality of life (QoL) from baseline to week 4

End point description:

Change in quality of life (QoL) from baseline to week 4.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in quality of life (QoL) 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	183	96		
Units: QoL score				
arithmetic mean (standard deviation)	-0.75 (± 7.09)	-0.82 (± 8.91)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9224
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.09428
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.81
upper limit	2
Variability estimate	Standard error of the mean
Dispersion value	0.9668

Secondary: Change in quality of life (QoL) from baseline to week 12

End point title	Change in quality of life (QoL) from baseline to week 12

End point description:

Change in quality of life (QoL) from baseline to week 12.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change in quality of life (QoL) from baseline to week 12.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	80		
Units: QoL score				
arithmetic mean (standard deviation)	-2.48 (± 6.67)	-1.45 (± 7.2)		

Statistical analyses

Statistical analysis title	Superiority tested by MMRM

Statistical analysis description:

The MMRM included treatment, visit, treatment*visit interactions, platinum based chemotherapy (Yes/No), and country as factors and baseline value as covariate.

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

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2527
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.9777
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.66
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.8515

Secondary: Change in restless legs syndrome (RLS) symptoms (RLS score) from baseline to week 12 in subjects with RLS symptoms at baseline

End point title	Change in restless legs syndrome (RLS) symptoms (RLS score) from baseline to week 12 in subjects with RLS symptoms at baseline

End point description:

Change in restless legs syndrome (RLS) symptoms (RLS score) from baseline to week 12 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 (RLS score) from baseline to week 12.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	1		
Units: RLS score				
arithmetic mean (full range (min-max))	-9 (-9 to -9)	11 (11 to 11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Impact of study drug on ability to complete chemotherapy assessed as yes or no response at 24 weeks

End point title	Impact of study drug on ability to complete chemotherapy assessed as yes or no response at 24 weeks

End point description:

Impact of study drug on ability to complete chemotherapy assessed as yes or no response at 24 weeks.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Impact of study drug on ability to complete chemotherapy assessed as yes or no response at 24 weeks.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	74		
Units: Yes/No response				
Yes, able to complete chemotherapy	147	69		
No, not able to complete chemotherapy	10	5		

Statistical analyses

Statistical analysis title	Superiority tested by Chi squared
Comparison groups	Group B, iron sulphate v Group A, iron isomaltoside 1000
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9112
Method	Chi-squared

Secondary: Impact of study drug on response to chemotherapy, assessed as complete remission, partial remission, stable remission, and progressive disease as per the investigator discretion at 24 weeks.

End point title	Impact of study drug on response to chemotherapy, assessed as complete remission, partial remission, stable remission, and progressive disease as per the investigator discretion at 24 weeks.

End point description:

Impact of study drug on response to chemotherapy, assessed as complete remission, partial remission, stable remission, and progressive disease as per the investigator discretion at 24 weeks.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Impact of study drug on response to chemotherapy, assessed as complete remission, partial remission, stable remission, and progressive disease as per the investigator discretion at 24 weeks.

End point values	Group A, iron isomaltoside 1000	Group B, iron sulphate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	74		
Units: Number of subjects				
Complete remission	41	19		
Partial remission	35	24		
Progressive disease	21	8		
Stable disease	60	23		

Statistical analyses

Statistical analysis title	Superiority tested by Chi squared
Comparison groups	Group A, iron isomaltoside 1000 v Group B, iron sulphate
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3909
Method	Chi-squared

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. The SAEs occurring after study termination were reported if considered related to the trial treatment.

Adverse event reporting additional description:

The investigator was responsible for ensuring that all AEs observed by the investigator or reported by the subjects 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	17.0

Reporting groups

Reporting group title	Group A, iron isomaltoside 1000

Reporting group description:

Subjects treated with iron isomaltoside 1000 were randomised to either an IV infusion (group A1) of maximum 1000 mg (the maximum dose per infusion was 1000 mg for subjects with a weight >45 kg, 750 mg for subjects with a weight between 35 and 45 kg, and 500 mg for subjects with a weight <35 kg) iron isomaltoside 1000 as single doses over approximately 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 approximately 2 minutes once weekly until full replacement dose was achieved (a total of 1-4 doses at a weekly interval).

Reporting group title	Group B, oral iron sulphate

Reporting group description:

Subjects receiving oral iron sulphate were treated daily for 12 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	32 / 229 (13.97%)	18 / 112 (16.07%)	
number of deaths (all causes)	11	10	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	8 / 229 (3.49%)	7 / 112 (6.25%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 7	0 / 7	
Malignant pleural effusion			
subjects affected / exposed	0 / 229 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metastases to lung			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 229 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 229 (0.44%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (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			
Anaphylactic reaction			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (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			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			

subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 229 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 229 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stridor			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram abnormal			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Post procedural complication			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 229 (1.31%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 229 (0.44%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 229 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	0 / 229 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 229 (0.87%)	2 / 112 (1.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenia			

subjects affected / exposed	2 / 229 (0.87%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 229 (0.44%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 229 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (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			

Fistula			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (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			
Pneumonia			
subjects affected / exposed	2 / 229 (0.87%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 112 (0.89%)	
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	0 / 229 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 229 (0.87%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 229 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 229 (0.44%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 229 (0.87%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

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	110 / 229 (48.03%)	58 / 112 (51.79%)	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 229 (8.73%)	12 / 112 (10.71%)	
occurrences (all)	22	13	
Leukopenia			
subjects affected / exposed	12 / 229 (5.24%)	10 / 112 (8.93%)	
occurrences (all)	13	13	
Neutropenia			
subjects affected / exposed	15 / 229 (6.55%)	6 / 112 (5.36%)	
occurrences (all)	21	9	
Thrombocytopenia			
subjects affected / exposed	11 / 229 (4.80%)	7 / 112 (6.25%)	
occurrences (all)	13	11	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	18 / 229 (7.86%)	7 / 112 (6.25%)	
occurrences (all)	20	9	
Pyrexia			
subjects affected / exposed	12 / 229 (5.24%)	4 / 112 (3.57%)	
occurrences (all)	13	4	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 229 (3.06%)	7 / 112 (6.25%)	
occurrences (all)	8	7	
Diarrhoea			
subjects affected / exposed	8 / 229 (3.49%)	10 / 112 (8.93%)	
occurrences (all)	14	11	

Faeces discoloured			
subjects affected / exposed	1 / 229 (0.44%)	9 / 112 (8.04%)	
occurrences (all)	1	9	
Nausea			
subjects affected / exposed	14 / 229 (6.11%)	8 / 112 (7.14%)	
occurrences (all)	19	12	
Stomatitis			
subjects affected / exposed	14 / 229 (6.11%)	5 / 112 (4.46%)	
occurrences (all)	14	5	
Vomiting			
subjects affected / exposed	16 / 229 (6.99%)	7 / 112 (6.25%)	
occurrences (all)	24	8	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	17 / 229 (7.42%)	9 / 112 (8.04%)	
occurrences (all)	17	9	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 229 (3.49%)	6 / 112 (5.36%)	
occurrences (all)	8	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2010	• Primary objective was changed to demonstrate that iron isomaltoside 1000 is non-inferior to iron sulphate • Endpoints were better defined to evaluate change in Hb and other iron parameters at defined time points during the study • An additional visit was added at 24 weeks • Iron dosage was increased to 2000 mg for subjects with body weight ≥ 100 kg
27 July 2010	• Duration of individual subject participation was clarified to be 24-26 weeks • Stratification criteria for Hb and s-ferritin was modified • The inclusion criteria was modified to clarify the types of non-myeloid malignancies
20 March 2013	• The primary objective was re-phrased to "ability to maintain haemoglobin concentration" • Measurement of TIBC was added as a secondary objective • The primary endpoint was modified from "change in Hb concentration from baseline to week 12" to "change in Hb concentration from baseline to week 4" • Additional secondary endpoint "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 • High grade lymphoma was added to inclusion criterion 2 • Exclusion criterion 10 was clarified and exclusion criterion 11 was deleted • Clarifications in drug dosage and formulation, study flowchart, study assessments, recording of vital signs, prohibited medications, protocol deviations, and reporting of AEs • Definition of non-smokers, statement on provision of study drug, storage temperature of study drug, description of overdose, and interim analyses were added • Changes in the statistical analyses were made as per changes in endpoints. MMRM was used instead of LOCF to account for missing values • Change in frequency of safety review meeting to once in 4 months

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported