Clinical trial results:
A randomized comparative, open-label study of intravenous iron isomaltoside 1000 (Monofer®) administered by high single dose infusions or standard medical care in women after postpartum haemorrhage

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-005782-12
Trial protocol	DK
Global end of trial date	16 December 2014

Results information

Result version number	v1 (current)
This version publication date	15 April 2016
First version publication date	15 April 2016

Trial information

Trial identification

Sponsor protocol code	P-Monofer-PP-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01895218
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 , Pharmacosmos A/S, +45 59485935, trial@pharmacosmos.com
Scientific contact	Clinical trial disclosure desk, Pharmacosmos A/S, 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	16 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 December 2014
Global end of trial reached?	Yes
Global end of trial date	16 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare efficacy of IV high single dose infusion of iron isomaltoside 1000 to standard medical care in women with PPH evaluated as physical fatigue.

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	03 May 2013
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	Denmark: 200
Worldwide total number of subjects	200
EEA total number of subjects	200

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)	200
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were screened in the period 03 May 2013 to 19 September 2015. The trial took place at one site in Denmark.

Pre-assignment

Screening details:

Women who were ≥18 years of age with PPH ≥ 700 and ≤ 1000 mL or PPH > 1000 mL and Hb > 6.5 g/dL (4.0 mmol/L) measured > 12 hours after delivery were able 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:

1200 mg iron isomaltoside 1000 was administered over approximately 15 min as a single IV infusion.

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:

1200 mg iron isomaltoside 1000 was administered over approximately 15 min as a single IV infusion. 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, standard care

Arm description:

Usually women with PPH are recommended to continue oral iron supplementation as recommended during pregnancy or to take 100 mg oral iron 1-2 times per day for a variable unspecified time period.

Arm type	standard care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Group A, iron isomaltoside 1000	Group B, standard care
Started	100	100
Completed	97	99
Not completed	3	1
Consent withdrawn by subject	2	-
Adverse event, non-fatal	1	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Group A, iron isomaltoside 1000
Reporting group description:	
1200 mg iron isomaltoside 1000 was administered over approximately 15 min as a single IV infusion.	
Reporting group title	Group B, standard care
Reporting group description:	
Usually women with PPH are recommended to continue oral iron supplementation as recommended during pregnancy or to take 100 mg oral iron 1-2 times per day for a variable unspecified time period.	

Reporting group values	Group A, iron isomaltoside 1000	Group B, standard care	Total
Number of subjects	100	100	200
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	32.2	32.6	
standard deviation	± 4.4	± 4.5	-
Gender categorical Units: Subjects			
Female	100	100	200
Male	0	0	0

Subject analysis sets	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set included all subjects who were randomised and received the trial drug	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS consisted of all randomised subjects, who received the trial drug, had a baseline physical fatigue score, and had at least 1 post-baseline physical fatigue score.	
Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population included all subjects in the FAS who did not have any major PDs (received 'rescue' allogenic RBC transfusion, received less than 80 % or more than 120 % of planned dose, or received prohibited concomitant medication during the trial).

Reporting group values	Safety analysis set	Full analysis set	Per protocol analysis set
Number of subjects	198	196	191
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 standard deviation	 32.3 ± 4.4	 32.4 ± 4.4	 32.3 ± 4.2
Gender categorical Units: Subjects			
Female Male	198 0	196 0	191 0

End points

End points reporting groups

Reporting group title	Group A, iron isomaltoside 1000
Reporting group description:	
1200 mg iron isomaltoside 1000 was administered over approximately 15 min as a single IV infusion.	
Reporting group title	Group B, standard care
Reporting group description:	
Usually women with PPH are recommended to continue oral iron supplementation as recommended during pregnancy or to take 100 mg oral iron 1-2 times per day for a variable unspecified time period.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set included all subjects who were randomised and received the trial drug	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS consisted of all randomised subjects, who received the trial drug, had a baseline physical fatigue score, and had at least 1 post-baseline physical fatigue score.	
Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population included all subjects in the FAS who did not have any major PDs (received 'rescue' allogenic RBC transfusion, received less than 80 % or more than 120 % of planned dose, or received prohibited concomitant medication during the trial).	

Primary: Aggregated change in physical fatigue score from baseline to week 12 (area under the curve (AUC)) in the 2 treatment arms measured by the Multidimensional Fatigue Inventory (MFI), FAS

End point title	Aggregated change in physical fatigue score from baseline to week 12 (area under the curve (AUC)) in the 2 treatment arms measured by the Multidimensional Fatigue Inventory (MFI), FAS
End point description:	
Aggregated change in physical fatigue score from baseline to week 12 (area under the curve (AUC)) in the 2 treatment arms measured by the Multidimensional Fatigue Inventory (MFI). Analysis performed on the FAS.	
End point type	Primary
End point timeframe:	
Aggregated change in physical fatigue score from baseline to week 12 (area under the curve (AUC)) in the 2 treatment arms	

End point values	Group A, iron isomaltoside 1000	Group B, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	99		
Units: Score				
arithmetic mean (standard deviation)	-3.47 (± 3.97)	-2.75 (± 2.82)		

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA) model

Statistical analysis description:

The primary endpoint was analysed using an analysis of covariance (ANCOVA) model, with treatment and PPH (700-1000 mL, >1000 mL) as factors and baseline MFI physical fatigue score as covariate. The estimated treatment differences (IV iron isomaltoside 1000 – standard medical care) expressed as contrasts of the adjusted means will be presented with corresponding 95 % CI and the p-value.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	-0.28

Primary: Aggregated change in physical fatigue score from baseline to week 12 (area under the curve (AUC)) in the 2 treatment arms measured by the Multidimensional Fatigue Inventory (MFI), PP

End point title	Aggregated change in physical fatigue score from baseline to week 12 (area under the curve (AUC)) in the 2 treatment arms measured by the Multidimensional Fatigue Inventory (MFI), PP

End point description:

Aggregated change in physical fatigue score from baseline to week 12 (area under the curve (AUC)) in the 2 treatment arms measured by the Multidimensional Fatigue Inventory (MFI).

Analysis performed on the PP analysis set.

End point type	Primary

End point timeframe:

Aggregated change in physical fatigue score from baseline to week 12 (area under the curve (AUC)) in the 2 treatment arms.

End point values	Group A, iron isomaltoside 1000	Group B, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	96		
Units: Score				
arithmetic mean (standard deviation)	-3.44 (± 3.98)	-2.71 (± 2.84)		

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA) model

Statistical analysis description:

The primary endpoint was analysed using an analysis of covariance (ANCOVA) model, with treatment and PPH (700-1000 mL, >1000 mL) as factors and baseline MFI physical fatigue score as covariate. The estimated treatment differences (IV iron isomaltoside 1000 – standard medical care) expressed as contrasts of the adjusted means will be presented with corresponding 95 % CI and the p-value.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0066
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	-0.27

Secondary: Change in haemoglobin from baseline to week 1

End point title	Change in haemoglobin from baseline to week 1

End point description:

Change in haemoglobin from baseline to week 1.

Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in haemoglobin from baseline to week 1.

End point values	Group A, iron isomaltoside 1000	Group B, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	97		
Units: g/dL				
arithmetic mean (standard deviation)	1.56 (± 0.76)	1.26 (± 0.92)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
The mixed model for repeated measurements (MMRM) included visit, treatment-by-visit, and PPH (700-1000 mL, >1000 mL) as factors, baseline value as covariate, and subject as random effect.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0198
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.51

Secondary: Change in haemoglobin from baseline to week 3

End point title	Change in haemoglobin from baseline to week 3
End point description:	
Change in haemoglobin from baseline to week 3. Analysis performed on FAS.	
End point type	Secondary
End point timeframe:	
Change in haemoglobin from baseline to week 3.	

End point values	Group A, iron isomaltoside 1000	Group B, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	97		
Units: g/dL				
arithmetic mean (standard deviation)	2.97 (± 0.99)	2.36 (± 1.11)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measurements (MMRM) included visit, treatment-by-visit, and PPH (700-1000 mL, >1000 mL) as factors, baseline value as covariate, and subject as random effect.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.84

Secondary: Change in haemoglobin from baseline to week 8

End point title	Change in haemoglobin from baseline to week 8

End point description:

Change in haemoglobin from baseline to week 8.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in haemoglobin from baseline to week 8.

End point values	Group A, iron isomaltoside 1000	Group B, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	99		
Units: g/dL				
arithmetic mean (standard deviation)	3.63 (± 1.36)	3.19 (± 1.27)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measurements (MMRM) included visit, treatment-by-visit, and PPH (700-1000 mL, >1000 mL) as factors, baseline value as covariate, and subject as random effect.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	0.67

Secondary: Change in haemoglobin from baseline to week 12

End point title	Change in haemoglobin from baseline to week 12

End point description:

Change in haemoglobin from baseline to week 12.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in haemoglobin from baseline to week 12.

End point values	Group A, iron isomaltoside 1000	Group B, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	95		
Units: g/dL				
arithmetic mean (standard deviation)	3.84 (± 1.53)	3.34 (± 1.42)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measurements (MMRM) included visit, treatment-by-visit, and PPH (700-1000 mL, >1000 mL) as factors, baseline value as covariate, and subject as random effect.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care

Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.73

Secondary: Change in s-ferritin from baseline to day 3

End point title	Change in s-ferritin from baseline to day 3

End point description:

Change in s-ferritin from baseline to day 3.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to day 3.

End point values	Group A, iron isomaltoside 1000	Group B, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	95		
Units: ng/mL				
arithmetic mean (standard deviation)	910.2 (± 329.2)	-2 (± 23.5)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measurements (MMRM) included visit, treatment-by-visit, and PPH (700-1000 mL, >1000 mL) as factors, baseline value as covariate, and subject as random effect.

Comparison groups	Group B, standard care v Group A, iron isomaltoside 1000
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	911.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	864.95
upper limit	958.42

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.
Analysis performed on 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, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	95		
Units: ng/mL				
arithmetic mean (standard deviation)	872.1 (± 336.7)	-11.3 (± 30.5)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measurements (MMRM) included visit, treatment-by-visit, and PPH (700-1000 mL, >1000 mL) as factors, baseline value as covariate, and subject as random effect.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	882.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	835.65
upper limit	928.96

Secondary: Change in s-ferritin from baseline to week 3

End point title	Change in s-ferritin from baseline to week 3

End point description:

Change in s-ferritin from baseline to week 3.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to week 3.

End point values	Group A, iron isomaltoside 1000	Group B, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	96		
Units: ng/mL				
arithmetic mean (standard deviation)	310.3 (± 166.6)	-28.4 (± 33.3)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measurements (MMRM) included visit, treatment-by-visit, and PPH (700-1000 mL, >1000 mL) as factors, baseline value as covariate, and subject as random effect.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	337.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	290.4
upper limit	383.72

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.

Analysis performed on 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, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	97		
Units: ng/mL				
arithmetic mean (standard deviation)	132.8 (± 107)	-29.9 (± 34.2)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measurements (MMRM) included visit, treatment-by-visit, and PPH (700-1000 mL, >1000 mL) as factors, baseline value as covariate, and subject as random effect.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	164.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	117.96
upper limit	210.93

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.
Analysis performed on 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, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	93		
Units: ng/mL				
arithmetic mean (standard deviation)	37 (± 22.3)	-31.9 (± 37.5)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
The mixed model for repeated measurements (MMRM) included visit, treatment-by-visit, and PPH (700-1000 mL, >1000 mL) as factors, baseline value as covariate, and subject as random effect.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	139.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	92.19
upper limit	186.02

Secondary: Change in transferrin saturation from baseline to day 3

End point title	Change in transferrin saturation from baseline to day 3
End point description:	
Change in transferrin saturation from baseline to day 3. Analysis performed on FAS.	
End point type	Secondary
End point timeframe:	
Change in transferrin saturation from baseline to day 3.	

End point values	Group A, iron isomaltoside 1000	Group B, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	94		
Units: Percentage				
arithmetic mean (standard deviation)	33.5 (± 21.5)	1.7 (± 9)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measurements (MMRM) included visit, treatment-by-visit, and PPH (700-1000 mL, >1000 mL) as factors, baseline value as covariate, and subject as random effect.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	31.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.5
upper limit	34.74

Secondary: Change in transferrin saturation from baseline to week 1

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

End point description:

Change in transferrin saturation from baseline to week 1.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to week 1.

End point values	Group A, iron isomaltoside 1000	Group B, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	93		
Units: Percentage				
arithmetic mean (standard deviation)	9.1 (± 8.6)	1.1 (± 8)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
The mixed model for repeated measurements (MMRM) included visit, treatment-by-visit, and PPH (700-1000 mL, >1000 mL) as factors, baseline value as covariate, and subject as random effect.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	7.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.62
upper limit	10.86

Secondary: Change in transferrin saturation from baseline to week 3	
End point title	Change in transferrin saturation from baseline to week 3
End point description:	
Change in transferrin saturation from baseline to week 3. Analysis performed on FAS.	
End point type	Secondary
End point timeframe:	
Change in transferrin saturation from baseline to week 3.	

End point values	Group A, iron isomaltoside 1000	Group B, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: Percentage				
arithmetic mean (standard deviation)	19 (± 9)	8.8 (± 11.7)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
The mixed model for repeated measurements (MMRM) included visit, treatment-by-visit, and PPH (700-1000 mL, >1000 mL) as factors, baseline value as covariate, and subject as random effect.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care

Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	10.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.28
upper limit	13.51

Secondary: Change in transferrin saturation from baseline to week 8

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

End point description:

Change in transferrin saturation from baseline to week 8.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to week 8.

End point values	Group A, iron isomaltoside 1000	Group B, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	97		
Units: Percentage				
arithmetic mean (standard deviation)	20.6 (± 10.3)	12.6 (± 12.5)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measurements (MMRM) included visit, treatment-by-visit, and PPH (700-1000 mL, >1000 mL) as factors, baseline value as covariate, and subject as random effect.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	7.96

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.86
upper limit	11.05

Secondary: Change in transferrin saturation from baseline to week 12

End point title	Change in transferrin saturation from baseline to week 12

End point description:

Change in transferrin saturation from baseline to week 12.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to week 12.

End point values	Group A, iron isomaltoside 1000	Group B, standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	93		
Units: Percentage				
arithmetic mean (standard deviation)	21.7 (± 10.6)	13.3 (± 11.5)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

The mixed model for repeated measurements (MMRM) included visit, treatment-by-visit, and PPH (700-1000 mL, >1000 mL) as factors, baseline value as covariate, and subject as random effect.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, standard care
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	8.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.35
upper limit	11.6

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time a subject had signed the informed consent form and until she had completed the trial, all AEs/SAEs were reported in the electronic case report form.

Adverse event reporting additional description:

An AE was described in the following manner: The nature of the event will be described in precise, standard medical terminology (i.e. not necessarily the exact words used by the subject). If known, a specific diagnosis was stated. Furthermore the Investigator described an AE regarding seriousness, severity, relatedness, and outcome.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Group A, iron isomaltoside 1000

Reporting group description:

1200 mg iron isomaltoside 1000 was administered over approximately 15 min as a single IV infusion.

Reporting group title	Group B, standard care

Reporting group description:

Usually women with PPH were recommended to continue oral iron supplementation as recommended during pregnancy or to take 100 mg oral iron 1-2 times per day for a variable unspecified time period.

Serious adverse events	Group A, iron isomaltoside 1000	Group B, standard care	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 98 (9.18%)	8 / 100 (8.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 98 (1.02%)	0 / 100 (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	0 / 98 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 98 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 98 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic pseudo-obstruction			
subjects affected / exposed	1 / 98 (1.02%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Galactostasis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	2 / 100 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis			
subjects affected / exposed	2 / 98 (2.04%)	2 / 100 (2.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 98 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mastitis			
subjects affected / exposed	4 / 98 (4.08%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 100 (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: 5 %

Non-serious adverse events	Group A, iron isomaltoside 1000	Group B, standard care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 98 (46.94%)	41 / 100 (41.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 98 (10.20%)	8 / 100 (8.00%)	
occurrences (all)	12	10	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	18 / 98 (18.37%)	19 / 100 (19.00%)	
occurrences (all)	18	19	
Haemorrhoids			
subjects affected / exposed	13 / 98 (13.27%)	8 / 100 (8.00%)	
occurrences (all)	13	8	
Infections and infestations			
Cystitis			
subjects affected / exposed	8 / 98 (8.16%)	3 / 100 (3.00%)	
occurrences (all)	8	4	
Fungal infection			
subjects affected / exposed	7 / 98 (7.14%)	3 / 100 (3.00%)	
occurrences (all)	8	3	
Mastitis			
subjects affected / exposed	7 / 98 (7.14%)	8 / 100 (8.00%)	
occurrences (all)	8	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2013	• In order to have a clear and robust primary endpoint, the primary endpoint was changed from change by visit to average aggregated change in physical fatigue score, i.e. calculated as the AUC of the change from baseline to last visit divided by sched-uled time from baseline to last visit. • In order to further strengthen the endpoints related to fatigue in the puerperal women, the postpartum questionnaire was included as an additional secondary efficacy end-point. • The maximum storage time for maternal milk samples was added in order to define the scope of the research bio-bank. • Drugs potentially yielding a decrease in oral iron absorption were deleted from the list of prohibited medication during the trial (for the standard medical care treatment group), as the aim of the standard medical care treatment group was to reflect clinical practice.
26 August 2013	• Inclusion criterion 1 was changed in order to align with current clinical practice: The minimum PPH was increased from 500 mL to 700 mL, and the minimum Hb concen-tration for subjects with PPH > 1000 mL was decreased from 8.0 g/dL (5.0 mmol/L) to 6.5 g/dL (4.0 mmol/L). • It was specified that only subjects living within a radius of 30 kilometres from the hospital were eligible for inclusion in the trial. This restriction was in order to ease the logistics associated with the visits in the subject's home. • Recording of anaemia and gastrointestinal symptoms was included as an additional objective and endpoint in order to investigate one of the main effects of iron deficiency as well as a well-known adverse effect of oral iron treatment, respectively, within the trial. • Visit windows were enlarged for visit 2 (from ±8 hours to ±1 day) and visit 5 (from ±2 days to ±1 week) in order to ensure full follow-up for as many subjects as possible. • It was specified that in cases where the infusion of iron isomaltoside 1000 was interrupted, it was allowed to restart the infusion after clinical assessment by the Principal Investigator or sub-investigator. • It was specified that admission to the maternity hotel was not considered to meet the regulatory definition for a SAE due to hospitalisation, and that admission of the new-born to the neonatal intensive care unit was evaluated case by case for seriousness.
11 February 2014	• Timing of maternal milk sample collection was changed from baseline, day 1, 2, and 3 to day 3 and week 1, and should be done in all subjects when possible. At the time of implementing this amendment, collection of milk samples from baseline and onwards had not been possible in any subjects. • It was specified that a 'current smoker' was defined as smoking within the last 6 months. • The reference document for SARs was changed from the SmPC to the IB for iron isomaltoside 1000, as the trial investigated a new indication for iron isomaltoside 1000. • It was specified that informed consent was obtained either by the investigator or by a project midwife.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported