Clinical trial results:
A randomized comparative, open-label study of intravenous iron isomaltoside 1000 (Monofer®) administered by high single dose infusions or red blood cell transfusion in women with severe postpartum iron deficiency anaemia

Summary

EudraCT number	2012-005783-10
Trial protocol	DK
Global end of trial date	04 July 2015

Results information

Result version number	v1 (current)
This version publication date	17 April 2016
First version publication date	17 April 2016

Trial information

Trial identification

Sponsor protocol code	P-Monofer-PP-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01895205
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	04 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 July 2015
Global end of trial reached?	Yes
Global end of trial date	04 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to get explorative information about IV high single dose infusion of iron isomaltoside 1000 compared to RBC transfusion in the treatment of severe PP-IDA 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	06 August 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: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	13
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were screened in the period 06 August 2013 to 12 April 2015. The trial took place at one site in Denmark.

Pre-assignment

Screening details:

Women who were ≥18 years of age with PPH > 1000 mL and Hb ≥ 5.5 and ≤ 8.0 g/dL (≥ 3.5 and ≤ 5.0 mmol/L) 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:

1500 mg iron isomaltoside 1000 (or 1000 mg in women with a pre-pregnancy weight below 45 kg) 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:

1500 mg iron isomaltoside 1000 (or 1000 mg in women with a pre-pregnancy weight below 45 kg) 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, RBC transfusion

Arm description:

Subjects received 1 or 2 units of red blood cells (RBC) administered at the baseline visit according to the hospital's standard operating procedure.

Arm type	RBC transfusion

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Group A, iron isomaltoside 1000	Group B, RBC transfusion
Started	7	6
Completed	7	6

Baseline characteristics

Reporting groups	
Reporting group title	Group A, iron isomaltoside 1000
Reporting group description:	
1500 mg iron isomaltoside 1000 (or 1000 mg in women with a pre-pregnancy weight below 45 kg) was administered over approximately 15 min as a single IV infusion.	
Reporting group title	Group B, RBC transfusion
Reporting group description:	
Subjects received 1 or 2 units of red blood cells (RBC) administered at the baseline visit according to the hospital's standard operating procedure.	

Reporting group values	Group A, iron isomaltoside 1000	Group B, RBC transfusion	Total
Number of subjects	7	6	13
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	30.4	34.5	
standard deviation	± 2.6	± 3.5	-
Gender categorical			
Units: Subjects			
Female	7	6	13
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 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 (i.e. did not receive 'rescue' allogenic RBC transfusion, did not receive less than 80 % or more than 120 % of planned dose, and did not receive prohibited concomitant medication during the trial).

Reporting group values	Safety analysis set	Full analysis set	Per protocol analysis set
Number of subjects	13	13	10
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	32.3	32.3	31.6
standard deviation	± 3.6	± 3.6	± 2.9
Gender categorical Units: Subjects			
Female	13	13	10
Male	0	0	0

End points

End points reporting groups

Reporting group title	Group A, iron isomaltoside 1000
Reporting group description:	
1500 mg iron isomaltoside 1000 (or 1000 mg in women with a pre-pregnancy weight below 45 kg) was administered over approximately 15 min as a single IV infusion.	
Reporting group title	Group B, RBC transfusion
Reporting group description:	
Subjects received 1 or 2 units of red blood cells (RBC) administered at the baseline visit according to the hospital's standard operating procedure.	
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 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 (i.e. did not receive 'rescue' allogenic RBC transfusion, did not receive less than 80 % or more than 120 % of planned dose, and did not receive 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)

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)
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, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: Score				
arithmetic mean (standard deviation)	-3.1 (± 3.75)	-3.71 (± 3.54)		

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 as factor and baseline MFI physical fatigue score as covariate. The estimated treat-ment differences (iron isomaltoside 1000 - RBC transfusion) expressed as contrasts of the adjusted means were presented with corresponding 95 % CI and the p-value for test of no treatment difference.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6051
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.28
upper limit	2.02

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, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	4		
Units: Score				
arithmetic mean (standard deviation)	-2.6 (± 3.84)	-4.54 (± 3.11)		

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 as factor and baseline MFI physical fatigue score as covariate. The estimated treat-ment differences (iron isomaltoside 1000 - RBC transfusion) expressed as contrasts of the adjusted means were presented with corresponding 95 % CI and the p-value for test of no treatment difference.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8475
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.26
upper limit	3.86

Secondary: Change in haemoglobin from baseline to day 1

End point title	Change in haemoglobin from baseline to day 1

End point description:

Change in haemoglobin from baseline to day 1.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in haemoglobin from baseline to day 1.

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: g/dL				
arithmetic mean (standard deviation)	-0.05 (± 0.77)	1.12 (± 0.55)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0411
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	-0.04

Secondary: Change in haemoglobin from baseline to day 2

End point title	Change in haemoglobin from baseline to day 2

End point description:

Change in haemoglobin from baseline to day 2.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in haemoglobin from baseline to day 2.

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: g/dL				
arithmetic mean (standard deviation)	0.21 (± 0.49)	1.2 (± 0.87)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0805
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.81
upper limit	0.11

Secondary: Change in haemoglobin from baseline to day 3

End point title	Change in haemoglobin from baseline to day 3

End point description:

Change in haemoglobin from baseline to day 3.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in haemoglobin from baseline to day 3.

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: g/dL				
arithmetic mean (standard deviation)	0.99 (± 1.07)	1.43 (± 1.02)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5134
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	0.65

Secondary: Change in haemoglobin from baseline to day 4

End point title	Change in haemoglobin from baseline to day 4
End point description:	
Change in haemoglobin from baseline to day 4. Analysis performed on FAS.	
End point type	Secondary
End point timeframe:	
Change in haemoglobin from baseline to day 4.	

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: g/dL				
arithmetic mean (standard deviation)	1.61 (± 1.23)	1.95 (± 0.8)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6753
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	0.76

Secondary: Change in haemoglobin from baseline to day 5

End point title	Change in haemoglobin from baseline to day 5
End point description:	
Change in haemoglobin from baseline to day 5. Analysis performed on FAS.	
End point type	Secondary
End point timeframe:	
Change in haemoglobin from baseline to day 5.	

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: g/dL				
arithmetic mean (standard deviation)	1.85 (± 1.27)	2.32 (± 0.78)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5633
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.26
upper limit	0.7

Secondary: Change in haemoglobin from baseline to day 6

End point title	Change in haemoglobin from baseline to day 6
End point description:	
Change in haemoglobin from baseline to day 6. Analysis performed on FAS.	
End point type	Secondary
End point timeframe:	
Change in haemoglobin from baseline to day 6.	

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: g/dL				
arithmetic mean (standard deviation)	2.3 (± 1.21)	2.58 (± 0.89)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8183
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	0.86

Secondary: Change in haemoglobin from baseline to day 7

End point title	Change in haemoglobin from baseline to day 7
End point description:	
Change in haemoglobin from baseline to day 7. Analysis performed on FAS.	
End point type	Secondary
End point timeframe:	
Change in haemoglobin from baseline to day 7.	

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: g/dL				
arithmetic mean (standard deviation)	2.07 (± 1.2)	3.24 (± 1)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.92
upper limit	0.08

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, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: g/dL				
arithmetic mean (standard deviation)	4.58 (± 0.88)	3.87 (± 1.22)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0295
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	2.07

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, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: g/dL				
arithmetic mean (standard deviation)	6.03 (± 1.55)	4.92 (± 1.34)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0122
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	2.21

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, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: g/dL				
arithmetic mean (standard deviation)	6.26 (± 1.33)	5.13 (± 1.32)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0115
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.22

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

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

End point description:

Change in s-ferritin from baseline to day 1.
Analysis performed on FAS

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to day 1.

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: ng/mL				
arithmetic mean (standard deviation)	308.4 (± 293.4)	-8.7 (± 20.4)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion

Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0156
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	399.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	84.4
upper limit	714.1

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

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

End point description:

Change in s-ferritin from baseline to day 2.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to day 2.

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: ng/mL				
arithmetic mean (standard deviation)	732 (± 330.1)	-14 (± 21.6)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	745.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	436.9
upper limit	1053.5

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, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: ng/mL				
arithmetic mean (standard deviation)	1065.5 (± 473.5)	-15.5 (± 23.3)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1087.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	776.1
upper limit	1398.6

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

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

End point description:

Change in s-ferritin from baseline to day 4.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to day 4.

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: ng/mL				
arithmetic mean (standard deviation)	1201.1 (± 435.8)	-17.2 (± 26)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1217.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	909.2
upper limit	1525.8

Secondary: Change in s-ferritin from baseline to day 5

End point title	Change in s-ferritin from baseline to day 5

End point description:

Change in s-ferritin from baseline to day 5.

Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to day 5.

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: ng/mL				
arithmetic mean (standard deviation)	1267.7 (± 344.2)	-19.8 (± 30.2)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1228.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	917.8
upper limit	1539.6

Secondary: Change in s-ferritin from baseline to day 6

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

End point description:

Change in s-ferritin from baseline to day 6.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to day 6.

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: ng/mL				
arithmetic mean (standard deviation)	1103.3 (± 499.1)	-19 (± 32.7)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM
Statistical analysis description:	
A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.	
Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1165.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	850.9
upper limit	1480.4

Secondary: Change in s-ferritin from baseline to day 7

End point title	Change in s-ferritin from baseline to day 7
End point description:	
Change in s-ferritin from baseline to day 7. Analysis performed on FAS.	
End point type	Secondary
End point timeframe:	
Change in s-ferritin from baseline to day 7.	

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: ng/mL				
arithmetic mean (standard deviation)	966 (± 411.5)	-12 (± 16.7)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1046.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	731.7
upper limit	1361.1

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, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: ng/mL				
arithmetic mean (standard deviation)	306.5 (± 109.7)	-44.6 (± 34)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0727
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	286.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29
upper limit	601.1

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, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: ng/mL				
arithmetic mean (standard deviation)	112.3 (± 59.1)	-44.5 (± 29.3)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3015
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	156
Confidence interval	
level	95 %
sides	2-sided
lower limit	-152.3
upper limit	464.3

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, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: ng/mL				
arithmetic mean (standard deviation)	95.3 (± 58.4)	-42.8 (± 31.8)		

Statistical analyses

Statistical analysis title	Test for superiority, MMRM

Statistical analysis description:

A mixed model for repeated measurements (MMRM) with treatment-by-visit as factor, baseline value as covariate, and subject as random effect was used.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, RBC transfusion
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3614
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	137.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-171
upper limit	445.6

Secondary: Change in transferrin saturation from baseline to day 1

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

End point description:

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

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to day 1.

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Percentage				
arithmetic mean (standard deviation)	119.2 (± 12.9)	-2.3 (± 3.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in transferrin saturation from baseline to day 2

End point title	Change in transferrin saturation from baseline to day 2

End point description:

Change in transferrin saturation from baseline to day 2.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to day 2.

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: Percentage				
arithmetic mean (standard deviation)	66.1 (± 12.1)	-2.2 (± 3.9)		

Statistical analyses

No statistical analyses for this end point

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, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Percentage				
arithmetic mean (standard deviation)	31 (± 8.8)	-2.5 (± 5.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in transferrin saturation from baseline to day 4

End point title	Change in transferrin saturation from baseline to day 4

End point description:

Change in transferrin saturation from baseline to day 4.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to day 4.

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: Percentage				
arithmetic mean (standard deviation)	17.4 (± 6.4)	-2 (± 4.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in transferrin saturation from baseline to day 5

End point title	Change in transferrin saturation from baseline to day 5

End point description:

Change in transferrin saturation from baseline to day 5.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to day 5.

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Percentage				
arithmetic mean (standard deviation)	9.5 (± 5.3)	-2 (± 5.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in transferrin saturation from baseline to day 6

End point title	Change in transferrin saturation from baseline to day 6

End point description:

Change in transferrin saturation from baseline to day 6.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to day 6.

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: Percentage				
arithmetic mean (standard deviation)	5.2 (± 4.4)	0.2 (± 1.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in transferrin saturation from baseline to day 7

End point title	Change in transferrin saturation from baseline to day 7

End point description:

Change in transferrin saturation from baseline to day 7.
Analysis performed on FAS.

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to day 7.

End point values	Group A, iron isomaltoside 1000	Group B, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: Percentage				
arithmetic mean (standard deviation)	9.3 (± 8.8)	-3.2 (± 5.4)		

Statistical analyses

No statistical analyses for this end point

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, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: Percentage				
arithmetic mean (standard deviation)	9.5 (± 3.3)	-0.8 (± 9.8)		

Statistical analyses

No statistical analyses for this end point

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, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: Percentage				
arithmetic mean (standard deviation)	16.9 (± 4.8)	4.2 (± 7.3)		

Statistical analyses

No statistical analyses for this end point

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, RBC transfusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: Percentage				
arithmetic mean (standard deviation)	15.9 (± 4.8)	3.8 (± 5.6)		

Statistical analyses

No statistical analyses for this end point

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:

1500 mg iron isomaltoside 1000 (or 1000 mg in women with a pre-pregnancy weight below 45 kg) was administered over approximately 15 min as a single IV infusion.

Reporting group title	Group B, RBC transfusion

Reporting group description:

Subjects received 1 or 2 units of red blood cells (RBC) administered at the baseline visit according to the hospital's standard operating procedure.

Serious adverse events	Group A, iron isomaltoside 1000	Group B, RBC transfusion	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
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, RBC transfusion	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	5 / 6 (83.33%)	

Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	2 / 6 (33.33%) 2	
General disorders and administration site conditions Application site discolouration subjects affected / exposed occurrences (all) Infusion site irritation subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1	 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 2 / 6 (33.33%) 2	
Gastrointestinal disorders Haemorrhoids subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	2 / 6 (33.33%) 2	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all)	 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0	 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1	
Infections and infestations			

Cystitis			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	
occurrences (all)	1	2	
Mastitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Vaginal infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2013	• The endpoint 'Change in other MFI fatigue symptoms' should be calculated from day 1 to day 2, 3, 4, 5, 6, and 7, week 3, 8, and 12. • It was specified that maternal milk iron level was to be assessed only in subjects ran-domised to iron isomaltoside 1000. • It was specified that assessment of anaemia and gastrointestinal symptoms should be performed at day 1, 3, and 7, week 3, 8, and 12. • It was specified that anaemia and gastrointestinal symptoms should be assessed by asking the subject if she had experienced any of the following symptoms: Palpitation, tinnitus, headache, dizziness, dyspnoea, nausea, vomiting, epigastric pain, thin feces, constipation, painful defecation, and symptomatic haemorrhoids. • Exclusion criteria number 7 was changed from 'Known decompensated liver cirrhosis and active hepatitis' to 'Known decompensated liver cirrhosis or active hepatitis' to correct a previous error. • Exclusion criteria number 10 was split into 2 different criteria. • To avoid selection bias, the geographical constraint on eligible subjects was changed from subjects living in the catchment area of Copenhagen University Hospital, Rigshospitalet to subjects living within a radius of 30 kilometres from the hospital. • It was added that in case the infusion of iron isomaltoside 1000 was interrupted, it would be allowed to restart the infusion after clinical assessment by the Principal In-vestigator or a sub investigator. • Table 2 of the protocol, summarising adverse events with IV iron, was updated ac-cording to the Monofer® SmPC. • 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 to be evaluated case by case for serious-ness. • The visit window for visit 2-8 (day 1-7) was enlarged from 18 hours to 1 day to ensure full follow-up of as many subjects as possible.
13 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 Monofer® SmPC to the IB for iron isomaltoside 1000, as the trial investigated a new indication for iron isomaltoside 1000. The implication of this change was negligible as the list of ex-pected side effects for iron isomaltoside 1000 was similar in the 2 documents. • It was specified that the data collection tool was an eCRF.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported