EU Clinical Trials Register

Clinical trial results:
Intravenous iron isomaltoside versus oral iron supplementation for treatment of iron deficiency in pregnancy: a randomised, comparative, open-label trial

Summary

EudraCT number	2017-000776-29
Trial protocol	DK
Global end of trial date	26 June 2020

Results information

Result version number	v1 (current)
This version publication date	24 June 2021
First version publication date	24 June 2021

Trial information

Trial identification

Sponsor protocol code	P-Monofer-PREG-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03188445
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	06 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 June 2020
Global end of trial reached?	Yes
Global end of trial date	26 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of intravenous (IV) iron isomaltoside compared with a fixed dose of oral iron administered as tablet ferrous fumarate with ascorbic acid as avoidance of developing/having iron deficiency anaemia (IDA) throughout the duration of the trial in pregnant women who experienced iron deficiency (ID) after 4 weeks of standard oral treatment.

Protection of trial subjects:

The protocol and amendments were approved by the local Ethics Committee and Competent Authority. The trial was conducted in accordance with good clinical practice (GCP) and the Declaration of Helsinki. Informed consent was obtained in writing prior to any trial-related activities.

Background therapy: -

Evidence for comparator:

Abbreviations used in this entry

ADR=Adverse drug reaction
AE=Adverse event
ALAT=Alanine aminotransferase
ASAT=Aspartate aminotransferase
FAS=Full analysis set
Fe-C=Ferrous fumarate with ascorbic acid
FSFV=First subject first visit
GCP=Good clinical practice
Hb=haemoglobin
IB=Investigator's Brochure
ICF=Informed consent form
ID=Iron Deficiency
IDA=Iron Deficiency Anaemia
ITT=Intention to treat
IV=Intravenous
LSFV=Last subject first visit
MMRM=Mixed model for repeated measures or Mixed mode analysis
SAE=serious adverse event
TSAT=Transferrin saturation
p=plasma
PP=Per protocol
RBC=Red blood cell
RLS=Restless legs syndrome
SAE=Serious adverse event
SAR=Serious adverse reaction
SmPC=Summary of Product Characteristics
SMQ=Standardised Medical Dictionary for Regulatory Activities Query
W=Week

Actual start date of recruitment	10 July 2017
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: 201
Worldwide total number of subjects	201
EEA total number of subjects	201

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)	201
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were screened in the period 10 July 2017 (FSFV date) to 28 February 2020 (LSFV date) according to the inclusion and exclusion criteria. The trial took place at one site in Denmark.

Pre-assignment

Screening details:

Women aged ≥18 years who were pregnant at gestation age 14+0 to 21+0 weeks and with p-ferritin <30 µg/L (0-29 µg/L) were allowed to participate in the trial after having signed the informed consent form.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Iron isomaltoside

Arm description:

Subjects received 1000 mg intravenous (IV) iron isomaltoside, administered as a single dose at baseline (if pre-pregnancy body weight <50 kg then 20 mg/kg pre-pregnancy body weight).

Arm type	Experimental
Investigational medicinal product name	Iron isomaltoside
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:

Iron isomaltoside was administered as a single IV infusion of 1000 mg at baseline (if pre-pregnancy body weight was <50 kg then 20 mg/kg pre-pregnancy body weight). The dose was diluted in 100 mL 0.9 % sodium chloride and administered over approximately 20 minutes.

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

Arm title	Oral iron (ferrous fumarate with ascorbic acid)

Arm description:

Subjects received one daily tablet containing 330 mg ferrous fumarate (equivalent to 100 mg elemental iron) and 60 mg ascorbic acid (vitamin C).

Arm type	Active comparator
Investigational medicinal product name	Ferrous fumarate with ascorbic acid
Investigational medicinal product code	B03AA02
Other name	Jern C
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One daily tablet containing 330 mg ferrous fumarate (equivalent to 100 mg elemental iron) and 60 mg ascorbic acid (vitamin C), for the duration of the trial.

Number of subjects in period 1	Iron isomaltoside	Oral iron (ferrous fumarate with ascorbic acid)
Started	100	101
Completed	93	89
Not completed	7	12
Consent withdrawn by subject	3	4
Adverse event, non-fatal	2	4
The subject gave birth before the final visit.	-	1
Lost to follow-up	2	3

Baseline characteristics

Reporting groups

Reporting group title	Iron isomaltoside

Reporting group description:

Subjects received 1000 mg intravenous (IV) iron isomaltoside, administered as a single dose at baseline (if pre-pregnancy body weight <50 kg then 20 mg/kg pre-pregnancy body weight).

Reporting group title	Oral iron (ferrous fumarate with ascorbic acid)

Reporting group description:

Subjects received one daily tablet containing 330 mg ferrous fumarate (equivalent to 100 mg elemental iron) and 60 mg ascorbic acid (vitamin C).

Reporting group values	Iron isomaltoside	Oral iron (ferrous fumarate with ascorbic acid)	Total
Number of subjects	100	101	201
Age categorical Units: Subjects			
Adults (18-64 years)	100	101	201
Age continuous Units: years			
arithmetic mean	30.7	31.3	
standard deviation	± 4.5	± 4.6	-
Gender categorical Units: Subjects			
Female	100	101	201

End points

End points reporting groups

Reporting group title	Iron isomaltoside
Reporting group description:	
Subjects received 1000 mg intravenous (IV) iron isomaltoside, administered as a single dose at baseline (if pre-pregnancy body weight <50 kg then 20 mg/kg pre-pregnancy body weight).	
Reporting group title	Oral iron (ferrous fumarate with ascorbic acid)
Reporting group description:	
Subjects received one daily tablet containing 330 mg ferrous fumarate (equivalent to 100 mg elemental iron) and 60 mg ascorbic acid (vitamin C).	

Primary: 1_Hb ≥11.0 g/dL (≥6.8 mmol/L) at all post-baseline time points, ITT

End point title	1_Hb ≥11.0 g/dL (≥6.8 mmol/L) at all post-baseline time points, ITT
End point description:	

Proportion of subjects who had Hb ≥11.0 g/dL (≥6.8 mmol/L) at all post-baseline time points (weeks 3, 6, 12, and 18). Subjects who achieved this Hb level are referred to responders; those subjects who did not achieved this Hb level are referred to as non-responders.

The analysis was performed using the results from the Intention to treat (ITT) analysis set.

End point type	Primary
End point timeframe:	

Post-baseline at weeks 3, 6, 12, and 18.

End point values	Iron isomaltoside	Oral iron (ferrous fumarate with ascorbic acid)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[1]	101[2]		
Units: Proportion of subjects				
Responders, completed without missing week 18	84	65		
Responders, not completed or missing week 18	7	10		
Non-responders	9	26		

Notes:

[1] - ITT Analysis set

[2] - ITT Analysis set

Statistical analyses

Statistical analysis title	Kaplan-Meier method
Statistical analysis description:	

The time to Hb <11 g/dL was estimated by a Kaplan-Meier curve using scheduled visits. Based on the Kaplan-Meier curve, the proportion of subjects who have met the primary endpoint (achievement/maintenance of Hb ≥11 g/dL at all post-baseline visits) at week 18 was estimated and compared between the treatment groups.

Comparison groups	Iron isomaltoside v Oral iron (ferrous fumarate with ascorbic acid)

Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Kaplan-Meier method
Parameter estimate	Risk difference (RD)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.101
upper limit	0.25

Secondary: 2_Haemoglobin - Change from baseline

End point title	2_Haemoglobin - Change from baseline

End point description:

Change in haemoglobin from baseline to prespecified days up to week 18 . The number of subjects included in the evaluation at each timepoint:

Iron Isomaltoside:
W3=98
W6= 93
W12=93
W18=92

Oral iron (ferrous fumarate with ascorbic acid):
W3=100
W6= 97
W12=94
W18=89

End point type	Secondary

End point timeframe:

Baseline to weeks 3, 6, 12, and 18.

End point values	Iron isomaltoside	Oral iron (ferrous fumarate with ascorbic acid)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[3]	101[4]		
Units: g/dL				
arithmetic mean (standard deviation)				
Week 3	0.07 (± 0.63)	-0.02 (± 0.53)		
Week 6	0.31 (± 0.67)	-0.16 (± 0.53)		
Week 12	0.47 (± 0.77)	0.09 (± 0.73)		
Week 18	0.71 (± 0.82)	0.54 (± 0.85)		

Notes:

[3] - ITT analysis set

[4] - ITT analysis set

Statistical analyses

Statistical analysis title	Week 3_Superiority tested by MMRM

Statistical analysis description:

The MMRM model included the fixed, categorical effects of treatment, strata, week, treatment-by-week interaction, as well as the continuous, fixed covariates of baseline Hb value and baseline Hb-by-week interaction.

The number of subjects in this analysis is N=198.

Comparison groups	Iron isomaltoside v Oral iron (ferrous fumarate with ascorbic acid)
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0628
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.3

Statistical analysis title	Week 6_Superiority tested by MMRM

Statistical analysis description:

The MMRM model included the fixed, categorical effects of treatment, strata, week, treatment-by-week interaction, as well as the continuous, fixed covariates of baseline Hb value and baseline Hb-by-week interaction.

The number of subjects in this analysis is N=190.

Comparison groups	Iron isomaltoside v Oral iron (ferrous fumarate with ascorbic acid)
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.69

Statistical analysis title	Week 12_Superiority tested by MMRM

Statistical analysis description:

The MMRM model included the fixed, categorical effects of treatment, strata, week, treatment-by-week interaction, as well as the continuous, fixed covariates of baseline Hb value and baseline Hb-by-week

interaction.

The number of subjects in this analysis is N=187.

Comparison groups	Iron isomaltoside v Oral iron (ferrous fumarate with ascorbic acid)
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.64

Statistical analysis title	Week 18_Superiority tested by MMRM

Statistical analysis description:

The MMRM model included the fixed, categorical effects of treatment, strata, week, treatment-by-week interaction, as well as the continuous, fixed covariates of baseline Hb value and baseline Hb-by-week interaction.

The number of subjects in this analysis is N=181.

Comparison groups	Iron isomaltoside v Oral iron (ferrous fumarate with ascorbic acid)
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0114
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.49

Secondary: 3_p-ferritin - Change from baseline

End point title	3_p-ferritin - Change from baseline

End point description:

Change in p-ferritin from baseline to prespecified days up to Week 18.
The number of subjects included in the evaluation at each timepoint:

Iron Isomaltoside:
W3=94
W6=90
W12=90
W18=88

Oral iron (ferrous fumarate with ascorbic acid):
W3=100
W6=97
W12=94
W18=89

End point type	Secondary

End point timeframe:
Baseline to weeks 3, 6, 12, and 18.

End point values	Iron isomaltoside	Oral iron (ferrous fumarate with ascorbic acid)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[5]	101[6]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 3	199.5 (± 65.3)	0.8 (± 8.5)		
Week 6	102.1 (± 39.8)	-1.3 (± 7.6)		
Week 12	31.7 (± 26.6)	5.2 (± 24.2)		
Week 18	12.3 (± 24.5)	10.1 (± 40.3)		

Notes:

[5] - ITT analysis set

[6] - ITT analysis set

Statistical analyses

Statistical analysis title	Week 3_Superiority tested by MMRM

Statistical analysis description:

The MMRM model included the fixed, categorical effects of treatment, strata, week, treatment-by week interaction, as well as the continuous, fixed covariates of baseline ferritin value and baseline ferritin-by week interaction.

The number of subjects in this analysis is N=194.

Comparison groups	Iron isomaltoside v Oral iron (ferrous fumarate with ascorbic acid)
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	199.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	186.9
upper limit	211.8

Statistical analysis title	Week 6_Superiority tested by MMRM

Statistical analysis description:

The MMRM model included the fixed, categorical effects of treatment, strata, week, treatment-by week interaction, as well as the continuous, fixed covariates of baseline ferritin value and baseline ferritin-by week interaction.

The number of subjects in this analysis is N=187.

Comparison groups	Iron isomaltoside v Oral iron (ferrous fumarate with ascorbic acid)
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	101.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	93.3
upper limit	109.8

Statistical analysis title	Week 12_Superiority tested by MMRM

Statistical analysis description:

The MMRM model included the fixed, categorical effects of treatment, strata, week, treatment-by week interaction, as well as the continuous, fixed covariates of baseline ferritin value and baseline ferritin-by week interaction.

The number of subjects in this analysis is N=184

Comparison groups	Iron isomaltoside v Oral iron (ferrous fumarate with ascorbic acid)
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	25.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.8
upper limit	32.7

Statistical analysis title	Week 18_Superiority tested by MMRM

Statistical analysis description:

The MMRM model included the fixed, categorical effects of treatment, strata, week, treatment-by week interaction, as well as the continuous, fixed covariates of baseline ferritin value and baseline ferritin-by week interaction.

The number of subjects in this analysis is N=177.

Comparison groups	Iron isomaltoside v Oral iron (ferrous fumarate with ascorbic acid)
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4975
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	13.1

Secondary: 4_TSAT - Change from baseline

End point title	4_TSAT - Change from baseline

End point description:

Change in TSAT from baseline to prespecified days up to Week 18. The number of subjects included in the evaluation at each timepoint:

Iron Isomaltoside:
W3=93
W6=88
W12=89
W18=87

Oral iron (ferrous fumarate with ascorbic acid):
W3=100
W6=96
W12=94
W18=89

End point type	Secondary

End point timeframe:

Baseline to weeks 3, 6, 12, and 18.

End point values	Iron isomaltoside	Oral iron (ferrous fumarate with ascorbic acid)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[7]	101[8]		
Units: Percent				
arithmetic mean (standard deviation)				
Week 3	10.16 (± 9.78)	1.39 (± 10.87)		
Week 6	5.94 (± 9.83)	0.25 (± 13.10)		
Week 12	-0.56 (± 9.83)	-0.38 (± 13.16)		
Week 18	-2.83 (± 10.82)	1.78 (± 13.75)		

Notes:

[7] - ITT analysis set

[8] - ITT analysis set

Statistical analyses

Statistical analysis title	Week 3_Superiority tested by MMRM

Statistical analysis description:

The MMRM model included the fixed, categorical effects of treatment, strata, week, treatment-by week interaction, as well as the continuous, fixed covariates of baseline TSAT value and baseline TSAT-by week interaction.

The number of subjects in this analysis is N=193.

Comparison groups	Iron isomaltoside v Oral iron (ferrous fumarate with ascorbic acid)
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.31
upper limit	11.49

Statistical analysis title	Week 6_Superiority tested by MMRM

Statistical analysis description:

The MMRM model included the fixed, categorical effects of treatment, strata, week, treatment-by week interaction, as well as the continuous, fixed covariates of baseline TSAT value and baseline TSAT-by week interaction.

The number of subjects in this analysis is N=184.

Comparison groups	Iron isomaltoside v Oral iron (ferrous fumarate with ascorbic acid)
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	5.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.06
upper limit	8.61

Statistical analysis title	Week 12_Superiority tested by MMRM

Statistical analysis description:

The MMRM model included the fixed, categorical effects of treatment, strata, week, treatment-by week interaction, as well as the continuous, fixed covariates of baseline TSAT value and baseline TSAT-by week interaction.

The number of subjects in this analysis is N=183.

Comparison groups	Iron isomaltoside v Oral iron (ferrous fumarate with ascorbic acid)
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6896
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.16
upper limit	2.1

Statistical analysis title	Week 18_Superiority tested by MMRM

Statistical analysis description:

The MMRM model included the fixed, categorical effects of treatment, strata, week, treatment-by week interaction, as well as the continuous, fixed covariates of baseline TSAT value and baseline TSAT-by week interaction.

The number of subjects in this analysis is N=176.

Comparison groups	Iron isomaltoside v Oral iron (ferrous fumarate with ascorbic acid)
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.59
upper limit	-1.98

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-treated subjects: All SAEs were reported from the time of signing the ICF to trial completion or discontinuation.

Treated subjects: All AEs and SAEs were reported from the time of signing the ICF to trial completion or discontinuation.

Adverse event reporting additional description:

The investigator described the nature of the AE/SAEs, using the standard medical terminology. If known, a specific diagnosis was stated.
The safety analysis set was used for evaluation of the AE/SAEs; safety analysis set = All subjects who received at least one dose of the trial drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Iron isomaltoside

Reporting group description:

Iron isomaltoside administered as a single IV infusion of 1000 mg at baseline (if pre-pregnancy body weight <50 kg then 20 mg/kg pre-pregnancy body weight).

Reporting group title	Oral iron (ferrous fumarate with ascorbic acid)

Reporting group description:

One daily tablet containing 330 mg ferrous fumarate (equivalent to 100 mg elemental iron) and 60 mg ascorbic acid (vitamin C).

Reporting group title	Oral iron/iron isomaltoside

Reporting group description:

Subjects who initially received oral ferrous fumarate with ascorbic (Fe-C) and later received additional treatment with IV iron isomaltoside.

For subjects in the oral iron/iron isomaltoside group, AEs starting at or after day of extra IV iron isomaltoside dose assessed as related or possible related to oral iron will be reported in the oral iron group whereas all other AEs will be reported in the oral iron/iron isomaltoside group after the first additional IV iron isomaltoside dose has been administered.

Serious adverse events	Iron isomaltoside	Oral iron (ferrous fumarate with ascorbic acid)	Oral iron/iron isomaltoside
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 99 (12.12%)	12 / 101 (11.88%)	2 / 15 (13.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Foetal monitoring abnormal			
subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	1 / 99 (1.01%)	0 / 101 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 99 (1.01%)	0 / 101 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Threatened labour			
subjects affected / exposed	2 / 99 (2.02%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pre-eclampsia			
subjects affected / exposed	1 / 99 (1.01%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion missed			
subjects affected / exposed	1 / 99 (1.01%)	0 / 101 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion spontaneous			
subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical incompetence			

subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Premature delivery			
subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Premature labour			
subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Premature rupture of membranes			
subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stillbirth			
subjects affected / exposed	1 / 99 (1.01%)	0 / 101 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine contractions during pregnancy			
subjects affected / exposed	0 / 99 (0.00%)	0 / 101 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 99 (0.00%)	0 / 101 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	1 / 99 (1.01%)	0 / 101 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 99 (1.01%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids thrombosed			
subjects affected / exposed	1 / 99 (1.01%)	0 / 101 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	1 / 99 (1.01%)	0 / 101 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	1 / 99 (1.01%)	0 / 101 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 99 (1.01%)	0 / 101 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Iron isomaltoside	Oral iron (ferrous fumarate with ascorbic acid)	Oral iron/iron isomaltoside
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 99 (96.97%)	97 / 101 (96.04%)	14 / 15 (93.33%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 99 (1.01%)	1 / 101 (0.99%)	2 / 15 (13.33%)
occurrences (all)	1	1	2
Pregnancy, puerperium and perinatal conditions			
Uterine contractions during pregnancy			
subjects affected / exposed	22 / 99 (22.22%)	16 / 101 (15.84%)	3 / 15 (20.00%)
occurrences (all)	23	16	3
Foetal hypokinesia			
subjects affected / exposed	13 / 99 (13.13%)	13 / 101 (12.87%)	3 / 15 (20.00%)
occurrences (all)	15	16	3
Foetal growth restriction			
subjects affected / exposed	5 / 99 (5.05%)	6 / 101 (5.94%)	0 / 15 (0.00%)
occurrences (all)	6	9	0
Polyhydramnios			
subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Large for dates baby			
subjects affected / exposed	0 / 99 (0.00%)	0 / 101 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	29 / 99 (29.29%)	19 / 101 (18.81%)	1 / 15 (6.67%)
occurrences (all)	30	19	1
Drug ineffective			
subjects affected / exposed	2 / 99 (2.02%)	15 / 101 (14.85%)	0 / 15 (0.00%)
occurrences (all)	2	15	0
Oedema peripheral			
subjects affected / exposed	4 / 99 (4.04%)	8 / 101 (7.92%)	1 / 15 (6.67%)
occurrences (all)	4	8	1
Oedema			
subjects affected / exposed	4 / 99 (4.04%)	7 / 101 (6.93%)	1 / 15 (6.67%)
occurrences (all)	4	7	1
Pyrexia			
subjects affected / exposed	3 / 99 (3.03%)	6 / 101 (5.94%)	0 / 15 (0.00%)
occurrences (all)	3	6	0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	20 / 99 (20.20%)	15 / 101 (14.85%)	1 / 15 (6.67%)
occurrences (all)	20	16	1
Vaginal haemorrhage			
subjects affected / exposed	5 / 99 (5.05%)	4 / 101 (3.96%)	0 / 15 (0.00%)
occurrences (all)	6	4	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 99 (2.02%)	6 / 101 (5.94%)	0 / 15 (0.00%)
occurrences (all)	2	6	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 99 (8.08%)	3 / 101 (2.97%)	0 / 15 (0.00%)
occurrences (all)	8	3	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 99 (0.00%)	2 / 101 (1.98%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Nervous system disorders			

Restless legs syndrome			
subjects affected / exposed	31 / 99 (31.31%)	21 / 101 (20.79%)	4 / 15 (26.67%)
occurrences (all)	31	22	5
Headache			
subjects affected / exposed	19 / 99 (19.19%)	15 / 101 (14.85%)	0 / 15 (0.00%)
occurrences (all)	19	15	0
Dizziness			
subjects affected / exposed	11 / 99 (11.11%)	9 / 101 (8.91%)	1 / 15 (6.67%)
occurrences (all)	11	9	1
Paraesthesia			
subjects affected / exposed	5 / 99 (5.05%)	2 / 101 (1.98%)	1 / 15 (6.67%)
occurrences (all)	6	2	1
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	5 / 99 (5.05%)	8 / 101 (7.92%)	0 / 15 (0.00%)
occurrences (all)	6	9	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	11 / 99 (11.11%)	15 / 101 (14.85%)	1 / 15 (6.67%)
occurrences (all)	11	16	1
Constipation			
subjects affected / exposed	5 / 99 (5.05%)	18 / 101 (17.82%)	0 / 15 (0.00%)
occurrences (all)	5	18	0
Dyspepsia			
subjects affected / exposed	10 / 99 (10.10%)	7 / 101 (6.93%)	1 / 15 (6.67%)
occurrences (all)	10	7	1
Abdominal pain			
subjects affected / exposed	9 / 99 (9.09%)	6 / 101 (5.94%)	0 / 15 (0.00%)
occurrences (all)	9	6	0
Abdominal pain lower			
subjects affected / exposed	6 / 99 (6.06%)	7 / 101 (6.93%)	1 / 15 (6.67%)
occurrences (all)	6	7	1
Diarrhoea			
subjects affected / exposed	5 / 99 (5.05%)	7 / 101 (6.93%)	0 / 15 (0.00%)
occurrences (all)	5	7	0
Vomiting			

subjects affected / exposed	4 / 99 (4.04%)	7 / 101 (6.93%)	1 / 15 (6.67%)
occurrences (all)	4	7	1
Abdominal pain upper			
subjects affected / exposed	3 / 99 (3.03%)	6 / 101 (5.94%)	3 / 15 (20.00%)
occurrences (all)	4	6	3
Haemorrhoids			
subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	5 / 99 (5.05%)	2 / 101 (1.98%)	1 / 15 (6.67%)
occurrences (all)	5	2	1
Rash			
subjects affected / exposed	5 / 99 (5.05%)	2 / 101 (1.98%)	0 / 15 (0.00%)
occurrences (all)	5	2	0
Rash pruritic			
subjects affected / exposed	0 / 99 (0.00%)	0 / 101 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	11 / 99 (11.11%)	14 / 101 (13.86%)	0 / 15 (0.00%)
occurrences (all)	11	14	0
Back pain			
subjects affected / exposed	12 / 99 (12.12%)	9 / 101 (8.91%)	1 / 15 (6.67%)
occurrences (all)	12	9	1
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	21 / 99 (21.21%)	25 / 101 (24.75%)	1 / 15 (6.67%)
occurrences (all)	26	27	1
Gastroenteritis			
subjects affected / exposed	3 / 99 (3.03%)	11 / 101 (10.89%)	1 / 15 (6.67%)
occurrences (all)	3	12	1
Urinary tract infection			
subjects affected / exposed	7 / 99 (7.07%)	6 / 101 (5.94%)	1 / 15 (6.67%)
occurrences (all)	8	10	1
Influenza			

subjects affected / exposed	8 / 99 (8.08%)	1 / 101 (0.99%)	0 / 15 (0.00%)
occurrences (all)	9	1	0
Cystitis			
subjects affected / exposed	2 / 99 (2.02%)	3 / 101 (2.97%)	1 / 15 (6.67%)
occurrences (all)	4	3	1
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 99 (0.00%)	3 / 101 (2.97%)	1 / 15 (6.67%)
occurrences (all)	0	4	1
Gingivitis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 101 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Streptobacillus infection			
subjects affected / exposed	1 / 99 (1.01%)	0 / 101 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	10 / 99 (10.10%)	7 / 101 (6.93%)	2 / 15 (13.33%)
occurrences (all)	11	7	2
Hypocalcaemia			
subjects affected / exposed	6 / 99 (6.06%)	7 / 101 (6.93%)	0 / 15 (0.00%)
occurrences (all)	7	10	0
Hypercalcaemia			
subjects affected / exposed	0 / 99 (0.00%)	2 / 101 (1.98%)	1 / 15 (6.67%)
occurrences (all)	0	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 May 2017	• Change of haemoglobin (Hb) intervals used for stratification of randomisation from 9.0 10.4 g/dL (mild) and 7.0-8.9 g/dL (moderate) to 9.0 10.4 g/dL (mild) and 6.5-8.9 g/dL (moderate). • Addition of strata as a factor in the logistic regression model used to analyse the primary endpoint and in the Mixed Model for Repeated Measures (MMRM) used to analyse the majority of the secondary efficacy endpoints. • Change of the definition of the safety analysis set from 'all randomised subjects who received at least one dose of the trial drugs' to 'all subjects who received at least one dose of the trial drugs'. • Specification that adverse event (AE) results were to be presented for the safety analysis set and that listings were also to be prepared for non-treatment emergent serious AEs (in non-exposed subjects and for the safety analysis set).
03 May 2017	• Addition to the introduction section of results from previous trials on the efficacy and safety of other IV iron solutions used during pregnancy as well as a discussion of the risk that the investigational product can cross placenta, and how that would influence the foetus, based on a request from the Danish Medicines Agency. • Change of exclusion criterion 7 from 'Decompensated liver cirrhosis or active hepatitis (defined as aspartate aminotransferase (ASAT) or alanine aminotransferase (ALAT) >3 times upper limit of normal for a pregnant woman at a given gestational age)' to 'Decompensated liver cirrhosis or active hepatitis (defined as ALAT >3 times upper limit of normal for a pregnant woman at a given gestational age)' and removal of ASAT from the laboratory safety assessments, since it was no longer clinical practice at the clinical site to measure ASAT. • Change of timepoint for collection of demography from the baseline to the screening visit, so it was possible to describe the population that failed screening. • Removal of compliance assessment by pill count at weeks 3 and 12. • Change of collected information on concomitant medication from generic name to brand name, and addition of route and frequency. • Specification that if vital signs were measured more than once in a given time interval, the lowest measurement of diastolic blood pressure for the period (including the simultaneously measured systolic blood pressure and heart rate) should be noted in the electronic case report form. • Addition of a definition of treatment emergent AEs and non-treatment emergent AEs, and specification that in non-treated subjects only serious AEs should be reported and that in treated subjects all AEs should be reported from the subject signed the informed consent form.

23 November 2017	• Change of inclusion criterion 3 from 'Hb <10.5 g/dL (6.5 mmol/L) and ferritin <30 µg/L after 4 weeks of standard treatment in a clinical setting' to 'Hb ≤10.5 g/dL (6.5 mmol/L) and ferritin <30 µg/L after 4 weeks of standard treatment in a clinical setting' in order to avoid rounding errors. The Hb cut off used to determine if intravenous (IV) iron isomaltoside was allowed at weeks 6 and/or 12 was changed accordingly. • Change of exclusion criterion 7 from 'Decompensated liver cirrhosis or active hepatitis (defined as ALAT >3 times upper limit of normal for a pregnant woman at a given gestational age)' to 'ALAT > 3 times upper limit of normal for a pregnant woman at a given gestational age (e.g. decompensated liver cirrhosis or active hepatitis)' since subjects with increased ALAT levels > 3 times upper limit of normal should not be enrolled even though they were not diagnosed with decompensated liver cirrhosis or active hepatitis. • Deletion of exclusion criterion 16 ('Inability to read and understand the Danish language') in order to increase the number of potential subjects. • Rewording of Hb intervals used for stratification of randomisation from 9.0 10.4 g/dL (mild) and 6.5-8.9 g/dL (moderate) to ≥9.0 g/dL and <9.0 g/dL. • Change of the Hb cut off used to determine if rescue red blood cell (RBC) transfusion was allowed from <6.9 g/dL to ≤6.9 g/dL to align with exclusion criterion 14. • Specification that if the subject was in daily treatment for e.g. allergy or asthma, this was not considered as premedication and could be continued also before administration of iron isomaltoside.
23 November 2017	• Deletion of the planned analysis of soluble transferrin receptor since it was not possible to establish collaboration with an external laboratory regarding this analysis. • Specification that a research bio-bank was to be established at the Department of Clinical Biochemistry, Hvidovre University Hospital, for storage of the hepcidin samples. • Replacement of a specific list of adverse drug reactions (ADRs) for iron isomaltoside with a reference to the current version of the Investigator's Brochure (IB) for iron isomaltoside, and specification that the current version of the IB for iron isomaltoside (instead of a specific version) should always be used to assess if a serious adverse reaction (SAR) was considered a suspected unexpected SAR in order to ensure that the newest data were available. • Change of trial population to not only include subjects with iron deficiency anaemia (IDA) but also subjects with iron deficiency (ID) without anaemia. The protocol title and several sections have been changed accordingly. • Change of primary objective from 'evaluate and compare the effect of IV iron isomaltoside to a fixed dose of oral iron administered as tablet ferrous fumarate with ascorbic acid as correction of anaemia in pregnant women who have IDA after 4 weeks of standard treatment' to 'evaluate the effect of IV iron isomaltoside compared to a fixed dose of oral iron administered as tablet ferrous fumarate with ascorbic acid as avoidance of developing/having IDA throughout the duration of the trial in pregnant women who have ID after 4 weeks of standard oral treatment'. • Change of the primary endpoint from 'Hb ≥11.0 g/dL at any time point within 6 weeks after beginning of treatment with trial drugs' to 'Hb ≥11.0 g/dL (≥6.8 mmol/L) at all post baseline time points' including statistical analysis of the primary endpoint. • Deletion of the secondary endpoint 'Time to response (achieve an Hb ≥11.0 g/dL)'.

23 November 2017	• Change of sample size from 140 to 200 subjects including change of the sample size calculation. • Change of inclusion criterion 2 from 'Pregnancy at gestational age 14 (+2 weeks)' to 'Pregnancy at gestational age 14+0 – 19+0'. • Change of inclusion criterion 3 from 'Hb ≤10.5 g/dL (6.5 mmol/L) and ferritin <30 µg/L after 4 weeks of standard treatment in a clinical setting' to 'Ferritin <30 µg/L (0-29 µg/L) after 4 weeks of standard treatment in a clinical setting'. • Merge of the screening and baseline visits and deletion of eligibility laboratory assessments. • Change of exclusion criteria 1, 7, and 8 to be based on history/known condition and clinical assessment instead of biochemical assessment. • Rewording of exclusion criteria 10, 11, and 12 in order to incorporate that the screening and baseline visits were merged. • Change of Hb intervals used for stratification of randomisation from ≥9.0 g/dL and <9.0 g/dL to <11 g/dL and ≥11 g/dL. • Change of the Hb requirement for when an additional dose of IV iron isomaltoside was allowed at weeks 6 and/or 12 from ≤10.5 g/dL (6.5 mmol/L) to Hb <11 g/dL (<6.8 mmol/L). • Change of definition of per protocol (PP) population in relation to RBC transfusion: Any RBC transfusion after randomisation should lead to exclusion from the PP population instead of only RBC transfusion before week 6.
17 July 2018	• Change of the endpoint on AEs of special interest from 'Number of AEs of special interest (i.e. hypersensitivity symptoms defined in Standardised Medical Dictionary for Regulatory Activities Query (SMQ) terms (including four additional terms) for definition of hypersensitivity events and specific gastrointestinal symptoms (constipation, diarrhoea, flatulence, nausea, vomiting, abdominal pain, dyspepsia, dysgeusia, and stool discoloration) at pre-specified time points in relation to administration of trial drug)' to 'Number of AEs of special interest (i.e. hypersensitivity symptoms defined in SMQ terms (including four additional terms) and specific gastrointestinal symptoms (constipation, diarrhoea, flatulence, nausea, vomiting, abdominal pain, dyspepsia, dysgeusia, and stool discoloration) observed at any time during the trial in both treatment groups'. • Change of inclusion criterion 2 from 'Pregnancy at gestational age 14+0 – 19+0' to ''Pregnancy at gestational age 14+0 – 21+0'. • Specification that all symptoms of hypersensitivity were to be collected during the trial period. • Specification that intake of oral iron was only allowed if it was included in multivitamins. Thus, oral iron as supplement per se was not allowed. • Change of the statistical analysis of restless legs syndrome (RLS) to a repeated measures logistic regression model with treatment, visit, stratum, and treatment by visit interaction as fixed effects and baseline value as covariate since RLS is a binary endpoint.
22 October 2019	• Specification that the final subject visit was defined as the week 18 visit, time of contact to health care facility due to onset of labour, or time of decision to induce labour, and that AEs were to be collected up until one of the criteria for final subject visit was fulfilled. • Specification that all 4 questions related to RLS must be answered 'yes' for RLS to be present. • Change of the reference document for iron isomaltoside from the current IB to the current Summary Product of Characteristics (SmPC), since iron isomaltoside is approved in Denmark and the dosing in the trial was within the approved label. • Specification that subjects with a good clinical practice (GCP) deviation of clinical or statistical significance were also to be excluded from the PP population. • Addition of statistical analysis for hypophosphatemia and exploratory endpoints. • Specification of statistical analyses for the secondary endpoints and for the safety analyses. • Specification that statistical analyses of secondary endpoints were to be performed including all data points/events and only including data points/events up to the time point where an additional dose of IV iron isomaltoside was received. • Expansion of the section on protocol deviations.

22 October 2019	• Addition of the endpoint 'Incidence of hypophosphatemia (defined as s phosphate <2 mg/dL) at any time post-baseline to week 18)'. • Change of the endpoint 'Reason for the additional IV iron isomaltoside dose (intolerance, non-compliance, lack of effect)' to 'Reason for the additional IV iron isomaltoside dose (non-compliance, lack of effect)'. • Change of the endpoint 'Number of subjects who received 1 or more allogenic RBC transfusions and the number of units of RBC-transfused per transfused subject from baseline to 7 days postpartum (medical record follow-up)' to 'Number of subjects who received 1 or more allogenic RBC-transfusions and the number of units of RBC-transfused per transfused subject from baseline to final subject visit'. • Change of the endpoint 'Compliance to treatment: at baseline in the IV group and at weeks 6 and 18 in oral group' to 'Compliance to treatment: at baseline in the IV group and by pill count at weeks 6 and 18 in oral group'. • Further specification and definition of the exploratory endpoints collected from the medical records of the mother and the newborn from the final subject visit until 7 days postpartum. • Specification that 200 subjects should be randomised. • Specification of the method for pill count at week 6. • Deletion of 'Any drug, which potentially yields a decrease in oral iron absorption (e.g. tetracycline, antacids, and cholestyramine)' from the list of prohibited medication and replacement with an advice not to use any drug, which potentially yielded a decrease in oral iron absorption (e.g. tetracycline, antacids, and cholestyramine) if possible. • Specification of overdose in the oral treatment group as a dose > + 10 %.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32843079