Clinical trial results:
A randomized, double-blinded, comparative trial comparing the incidence of hypophosphatemia in relation to repeated treatment courses of iron isomaltoside and ferric carboxymaltose in subjects with iron deficiency anaemia due to inflammatory bowel disease

Summary

EudraCT number	2017-002452-87
Trial protocol	DK GB AT SE DE
Global end of trial date	25 May 2020

Results information

Result version number	v1 (current)
This version publication date	26 May 2021
First version publication date	26 May 2021

Trial information

Trial identification

Sponsor protocol code	P-Monofer-IBD-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03466983
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	04 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 May 2020
Global end of trial reached?	Yes
Global end of trial date	25 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the incidence of hypophosphatemia in subjects with iron deficiency anaemia (IDA) due to inflammatory bowel disease (IBD), treated with iron isomaltoside or ferric carboxymaltose.

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 (GCP) and the Declaration of Helsinki. Informed consent was obtained in writing prior to any trial-related activities.

Background therapy:

None.

Evidence for comparator:

Abbreviations used in this study entry

AE=Adverse event
D=Day
eGFR=Estimated Glomerular Filtration Rate
GCP=Good Clinical Practice
IBD=Inflammatory bowel disease
ICF=Informed consent form
IDA=Iron deficiency anaemia
ITT=Intention to treat
IV=Intravenous
SAE=Serious adverse event
TSAT=Transferrin saturation
W=Week

Actual start date of recruitment	23 May 2018
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	United Kingdom: 18
Country: Number of subjects enrolled	Austria: 42
Country: Number of subjects enrolled	Denmark: 22
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Sweden: 2
Worldwide total number of subjects	97
EEA total number of subjects	97

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)	88
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were screened from 23 May 2018 to 13 March 2020 according to the inclusion and exclusion criteria. The trial took place at 20 sites in 5 countries (Austria, Denmark, Germany, Sweden, United Kingdom).

Pre-assignment

Screening details:

Men and women aged ≥18 years with IBD and with Hb <13 g/dL, body weight ≥50 kg, s-ferritin ≤100 ng/mL, eGFR ≥65 mL/min/1.73 m2, s-phosphate >2.5 mg/dL, and where oral iron preparations were ineffective or could not be used or where there was a clinical need to deliver iron rapidly, were allowed to participate after signing the ICF.

Period 1

Period 1 title	Overall trial period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Blinding was obtained by shielding the subjects and blinded members of staff from seeing preparation of the trial drug and by having unblinded trial personnel not involved in any trial assessments responsible for preparing the trial drug. All used material was removed by the unblinded member of staff without revealing the treatment. Further this unblinded member of staff was the only one doing trial drug accountability. Trial drug accountability was monitored by an unblinded Monitor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A, iron isomaltoside

Arm description:

Iron isomaltoside was administered as a single IV infusion of 1000 mg at baseline and 500 mg or 1000 mg at day 35.

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 and 500 mg or 1000 mg at day 35 diluted in 0.9 % sodium chloride to a total volume of 100 mL (cumulative dose: 1500 mg or 2000 mg, respectively).

Iron isomaltoside is supplied 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, ferric carboxymaltose

Arm description:

Ferric carboxymaltose was administered as a single IV infusion of 1000 mg at baseline and 500 mg or 1000 mg at day 35.

Arm type	Active comparator

Investigational medicinal product name	Ferric carboxymaltose
Investigational medicinal product code	ATC code: B03AC
Other name	Ferinject
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ferric carboxymaltose was administered as a single IV infusion of 1000 mg at baseline and 500 mg or 1000 mg at day 35 diluted in 0.9 % sodium chloride to a total volume of 100 mL (cumulative dose: 1500 mg or 2000 mg, respectively).

Ferric carboxymaltose is supplied as a dark brown, sterile, aqueous, isotonic colloidal solution for IV injection.

Number of subjects in period 1	Group A, iron isomaltoside	Group B, ferric carboxymaltose
Started	49	48
Completed	44	42
Not completed	5	6
Consent withdrawn by subject	1	2
Physician decision	-	2
Adverse event, non-fatal	3	1
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Group A, iron isomaltoside
Reporting group description:	
Iron isomaltoside was administered as a single IV infusion of 1000 mg at baseline and 500 mg or 1000 mg at day 35.	
Reporting group title	Group B, ferric carboxymaltose
Reporting group description:	
Ferric carboxymaltose was administered as a single IV infusion of 1000 mg at baseline and 500 mg or 1000 mg at day 35.	

Reporting group values	Group A, iron isomaltoside	Group B, ferric carboxymaltose	Total
Number of subjects	49	48	97
Age categorical Units: Subjects			
Adults (18-64 years)	44	44	88
From 65-84 years	5	4	9
Age continuous Units: years			
arithmetic mean	42.4	41.7	
standard deviation	± 14.0	± 14.9	-
Gender categorical Units: Subjects			
Female	27	24	51
Male	22	24	46

End points

End points reporting groups

Reporting group title	Group A, iron isomaltoside
Reporting group description:	
Iron isomaltoside was administered as a single IV infusion of 1000 mg at baseline and 500 mg or 1000 mg at day 35.	
Reporting group title	Group B, ferric carboxymaltose
Reporting group description:	
Ferric carboxymaltose was administered as a single IV infusion of 1000 mg at baseline and 500 mg or 1000 mg at day 35.	
Subject analysis set title	Group A, iron isomaltoside
Subject analysis set type	Safety analysis
Subject analysis set description:	
Iron isomaltoside was administered as a single IV infusion of 1000 mg at baseline and 500 mg or 1000 mg at day 35.	
Subject analysis set title	Group B, ferric carboxymaltose
Subject analysis set type	Safety analysis
Subject analysis set description:	
Ferric carboxymaltose was administered as a single IV infusion of 1000 mg at baseline and 500 mg or 1000 mg at day 35.	

Primary: 1_Hypophosphatemia (s-phosphate <2 mg/dL)

End point title	1_Hypophosphatemia (s-phosphate <2 mg/dL)
End point description:	
Incidence of hypophosphatemia (defined as s-phosphate <2 mg/dL) occurring at any time from baseline to day 35.	
End point type	Primary
End point timeframe:	
From baseline to day 35.	

End point values	Group A, iron isomaltoside	Group B, ferric carboxymaltose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48[1]	49[2]		
Units: Subjects				
Subjects with hypophosphatemia	4	25		

Notes:

[1] - Safety analysis set

[2] - Safety analysis set

Statistical analyses

Statistical analysis title	Group A vs Group B
Statistical analysis description:	
Iron isomaltoside was compared with ferric carboxymaltose, by estimation of the risk difference and the associated 95 % Newcombe CI, adjusting for strata (screening s-phosphate level (< or ≥3.5 mg/dL)), using the Cochran-Mantel-Haenszel method.	
Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-42.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.1
upper limit	-24.6

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 10 . The number of subjects included in the evaluation at each timepoint:

Iron Isomaltoside
D1 N=48
W1 N=45
W2 N=46
W5 N=42
W6 N=43
W7 N=42
W10 N=43

Ferric Carboxymaltose
D1 N=48
W1 N=44
W2 N=47
W5 N=44
W6 N=41
W7 N=43
W10 N=41

End point type	Secondary

End point timeframe:

Baseline to Week 10 (Day 1, Week 1, 2, 5, 6, 7, 10)

End point values	Group A, iron isomaltoside	Group B, ferric carboxymaltose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[3]	48[4]		
Units: g/dL				
arithmetic mean (standard deviation)				
Day 1	0.13 (± 0.45)	-0.01 (± 0.50)		
Week 1	0.58 (± 0.73)	0.47 (± 0.71)		
Week 2	1.16 (± 0.87)	1.18 (± 0.94)		
Week 5	1.77 (± 1.01)	1.84 (± 1.06)		
Week 6	2.08 (± 1.07)	2.06 (± 1.13)		

Week 7	2.36 (± 1.27)	2.38 (± 1.23)		
Week 10	2.51 (± 1.41)	2.44 (± 1.49)		

Notes:

[3] - ITT

[4] - ITT

Statistical analyses

Statistical analysis title	Day 1

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix was used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1165
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.151
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.038
upper limit	0.341

Statistical analysis title	Week 1

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix was used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2293
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.152
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.097
upper limit	0.402

Statistical analysis title	Week 2

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix was used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9393
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.283
upper limit	0.305

Statistical analysis title	Week 5

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix was used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7778
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.427
upper limit	0.321

Statistical analysis title	Week 6

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix was used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8295
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.338
upper limit	0.42

Statistical analysis title	Week 7

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix was used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6428
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.102
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.335

Statistical analysis title	Week 10

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix was used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9257
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.026

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.573
upper limit	0.521

Secondary: 3_s-ferritin - Change from baseline

End point title	3_s-ferritin - Change from baseline

End point description:

Change in s-ferritin from baseline to prespecified days up to Week 10.

The number of subjects included in the evaluation at each timepoint:
Iron Isomaltoside
D1 N=48
W1 N=46
W2 N=46
W5 N=43
W6 N=42
W7 N=42
W10 N=45

Ferric Carboxymaltose
D1 N=47
W1 N=46
W2 N=47
W5 N=44
W6 N=42
W7 N=42
W10 N=42

End point type	Secondary

End point timeframe:

Baseline to Week 10 (Day 1, Week 1, 2, 5, 6, 7, 10)

End point values	Group A, iron isomaltoside	Group B, ferric carboxymaltose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[5]	48[6]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	107.98 (± 108.04)	148.03 (± 119.34)		
Week 1	350.55 (± 151.47)	473.78 (± 244.27)		
Week 2	192.86 (± 91.51)	204.19 (± 118.69)		
Week 5	70.73 (± 51.46)	65.07 (± 70.65)		
Week 6	272.56 (± 176.61)	325.75 (± 188.84)		
Week 7	196.36 (± 159.68)	206.39 (± 140.33)		

Week 10	127.13 (± 130.70)	116.16 (± 101.75)		

Notes:

[5] - ITT analysis set

[6] - ITT analysis set

Statistical analyses

Statistical analysis title	Day 1

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0951
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-39.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-87.05
upper limit	7.11

Statistical analysis title	Week 1

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0054
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-117.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-199.43
upper limit	-35.58

Statistical analysis title	Week 2

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6104
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-11.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.11
upper limit	32.54

Statistical analysis title	Week 5

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6214
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	6.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.2
upper limit	31.96

Statistical analysis title	Week 6

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.105
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-61.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-136.84
upper limit	13.18

Statistical analysis title	Week 7

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5274
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-19.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-82.56
upper limit	42.59

Statistical analysis title	Week 10

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7659
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	7.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.85
upper limit	56.66

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 10. The number of subjects included in the evaluation at each timepoint:

Iron Isomaltoside
D1 N=47
W1 N=45
W2 N=44
W5 N=41
W6 N=41
W7 N=40
W10 N=43

Ferric Carboxymaltose
D1 N=47
W1 N=45
W2 N=46
W5 N=44
W6 N=40
W7 N=42
W10 N=41

End point type	Secondary

End point timeframe:

Baseline to Week 10 (Day 1, Week 1, 2, 5, 6, 7, 10)

End point values	Group A, iron isomaltoside	Group B, ferric carboxymaltose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[7]	48[8]		
Units: percent				
arithmetic mean (standard deviation)				
Day 1	145.93 (± 46.40)	104.09 (± 27.42)		
Week 1	19.74 (± 15.36)	15.59 (± 11.52)		
Week 2	14.04 (± 9.16)	13.02 (± 8.96)		
Week 5	13.67 (± 10.46)	10.82 (± 9.78)		
Week 6	22.65 (± 14.82)	20.09 (± 18.79)		
Week 7	17.10 (± 12.89)	17.33 (± 10.82)		
Week 10	15.84 (± 12.79)	15.97 (± 13.83)		

Notes:

[7] - ITT Analysis set

[8] - ITT Analysis set

Statistical analyses

Statistical analysis title	Day 1

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	42.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	26.03
upper limit	58.08
Variability estimate	Standard error of the mean

Statistical analysis title	Week 1

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1822
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	4.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.04
upper limit	10.54
Variability estimate	Standard error of the mean

Statistical analysis title	Week 2

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors.

Comparison groups	Group B, ferric carboxymaltose v Group A, iron isomaltoside
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.809
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.55
upper limit	4.54
Variability estimate	Standard error of the mean

Statistical analysis title	Week 5

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2011
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	2.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.62
upper limit	7.58
Variability estimate	Standard error of the mean

Statistical analysis title	Week 6

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6704
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.96
upper limit	9.22
Variability estimate	Standard error of the mean

Statistical analysis title	Week 7

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors.

Comparison groups	Group B, ferric carboxymaltose v Group A, iron isomaltoside
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8795
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.79
upper limit	5.58
Variability estimate	Standard error of the mean

Statistical analysis title	Week 10

Statistical analysis description:

The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors.

Comparison groups	Group A, iron isomaltoside v Group B, ferric carboxymaltose

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8988
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.53
upper limit	6.28
Variability estimate	Standard error of the mean

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of signing the ICF and 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.

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	20.1

Reporting groups

Reporting group title	Group A, iron isomaltoside

Reporting group description:

Iron isomaltoside was administered as a single IV infusion of 1000 mg at baseline and 500 mg or 1000 mg at day 35.

Reporting group title	Group B, ferric carboxymaltose

Reporting group description:

Ferric carboxymaltose was administered as a single IV infusion of 1000 mg at baseline and 500 mg or 1000 mg at day 35.

Serious adverse events	Group A, iron isomaltoside	Group B, ferric carboxymaltose	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 48 (10.42%)	6 / 49 (12.24%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			

subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	1 / 48 (2.08%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal ulcer haemorrhage			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess neck			

subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group A, iron isomaltoside	Group B, ferric carboxymaltose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 48 (91.67%)	44 / 49 (89.80%)	
Investigations			
Blood phosphorus decreased			
subjects affected / exposed	2 / 48 (4.17%)	4 / 49 (8.16%)	
occurrences (all)	2	4	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 48 (0.00%)	3 / 49 (6.12%)	
occurrences (all)	0	3	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 48 (18.75%)	5 / 49 (10.20%)	
occurrences (all)	11	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 48 (10.42%)	4 / 49 (8.16%)	
occurrences (all)	5	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 48 (12.50%)	1 / 49 (2.04%)	
occurrences (all)	6	1	
Diarrhoea			
subjects affected / exposed	4 / 48 (8.33%)	2 / 49 (4.08%)	
occurrences (all)	5	4	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 48 (6.25%)	0 / 49 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 48 (8.33%)	2 / 49 (4.08%)	
occurrences (all)	5	2	
Urticaria			
subjects affected / exposed	4 / 48 (8.33%)	0 / 49 (0.00%)	
occurrences (all)	5	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 48 (14.58%)	6 / 49 (12.24%)	
occurrences (all)	12	7	
Pain in extremity			
subjects affected / exposed	1 / 48 (2.08%)	3 / 49 (6.12%)	
occurrences (all)	1	4	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 48 (16.67%)	10 / 49 (20.41%)	
occurrences (all)	9	11	
Influenza			
subjects affected / exposed	4 / 48 (8.33%)	3 / 49 (6.12%)	
occurrences (all)	5	3	
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	11 / 48 (22.92%)	17 / 49 (34.69%)	
occurrences (all)	11	18	
Hypophosphataemia			
subjects affected / exposed	0 / 48 (0.00%)	14 / 49 (28.57%)	
occurrences (all)	0	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 September 2017	• Change of exclusion criterion 20 from 'Pregnant or nursing women. In order to avoid pregnancy, women of childbearing potential have to use adequate contraception (e.g. intrauterine devices, hormonal contraceptives, or double barrier method) during the whole trial period and 7 days after the last dosing' to 'Pregnant or nursing women. In order to avoid pregnancy, women of childbearing potential have to use highly efficient contraception (e.g. intrauterine devices, hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release)) during the whole trial period and 7 days after the last dosing. A sterile sole partner or sexual abstinence is also considered acceptable provided it reflects the usual and preferred lifestyle of the participant' due to a requirement from the Competent Authority in Denmark.
06 November 2017	• Deletion of the exclusion criterion 'Active malignant disease, disease-free for less than 5 years' since exclusion of oncology patients was a mistake. • Deletion of the stratification based on type of underlying disease, as this was originally included in the protocol by mistake. • Correction of the volume of ferric carboxymaltose single-use vials from 15 mL to 20 mL in order to align with the available vial size. • Clarification that dilution of iron isomaltoside and ferric carboxymaltose was to a total volume of 100 mL instead of in 100 mL 0.9 % sodium chloride. • Clarification that the Ferinject® SmPC was the only reference document for choice of dose, investigational product administration, and SUSAR definition for ferric carboxymaltose. • Specification of TCT members (change from 'QC/Regulatory' to 'Quality Assurance', 'Quality Control', and 'Regulatory') in order to reflect the current TCT members.

06 November 2017	• Change of trial design from open-label to double-blind in order to increase the scientific value of the trial. • Change of inclusion criteria 3 and 4 from 'Hb < 10 g/dL' and 'Body weight > 70 kg' to 'Hb < 13 g/dL' and 'Body weight ≥ 50 kg' in order to be able to include subjects with a need of a cumulative dose of 1500 mg iron and obtain information on the safety and efficacy of iron isomaltoside in this group of subjects. • Addition of exclusion criterion 2 'Hb ≥ 10 g/dL and body weight < 70 kg' in order to ensure an iron need of minimum 1500 mg. • Change of dosing regimen from 1000 mg at baseline and at day 35 to 1000 mg at baseline and 500 or 1000 mg at day 35, i.e. the cumulative dose was changed from 2000 mg to 1500 or 2000 mg, in order to be able to include subjects with a need of a cumulative dose of 1500 mg iron. • Specification that the cumulative dose of 1500 or 2000 mg was dependent on the subject's screening Hb and body weight. • Change of infusion time for ferric carboxymaltose from at least 15 minutes to approximately 20 minutes. • Deletion of the exclusion criterion 'History of a psychological illness or seizures' since no contraindications or warnings related to psychological illness or seizures are included in the SmPC. • Deletion of the visit at week 13, thereby having week 10 as the last visit, in order to ease the burden on the subjects. • Addition of ESAs, radiotherapy, and chemotherapy to the list of prohibited medication and non-drug therapies in order to ensure alignment with the exclusion criteria. • Deletion of the measurement of pyridinoline in urine, since this was an exploratory endpoint with a limited value, which showed to be quite challenging to both site and subjects due to very specific requirements of the urine sample. • Clarification that alkaline phosphatase was measured in serum rather than in plasma.
12 January 2018	• The following was added as a note to exclusion criterion 2 for clarification: 'To ensure an iron need of minimum 1500 mg; subjects with a Hb ≥ 10 g/dL must have a body weight ≥ 70 kg. Subjects with a body weight of ≥ 50 kg to < 70 kg are eligible only if Hb is below 10 mg/dL.' • In addition to the urine pregnancy test at baseline in all women of childbearing potential, a serum pregnancy test was added at screening and baseline for all women of childbearing potential enrolled in UK due to a requirement from the Competent Authority in UK.
22 January 2018	• Deletion of the exclusion criterion 'Vitamin D deficiency' and deletion of vitamin D from the eligibility laboratory assessments, since it is not standard clinical practice to measure vitamin D prior to IV iron treatment. • Addition of details related to the blinding and randomisation procedures.

15 July 2019	• Clarification that exploratory safety endpoints were to be analysed using the safety analysis set, while exploratory efficacy endpoints were to be analysed using the ITT analysis set. • Clarification that for the statistical analyses of change from baseline in Hb, s-ferritin, and TSAT, subjects without post-baseline assessments were to have change from baseline = 0 imputed at the first post-baseline visit. • Change of exclusion criterion 7 from 'Treatment with erythropoietin or ESAs, red blood cell transfusion, radiotherapy, and/or chemotherapy within the last 30 days prior to screening' to 'Treatment with erythropoietin or ESAs, red blood cell transfusion, radiotherapy, and/or chemotherapy (except immune modulating therapy for standard IBD treatment) within the last 30 days prior to screening' for clarification. • The following clarifications were made to the list of prohibited medication: 'Any iron supplementation other than investigational drug (nutritional supplementation including iron is allowed unless it is assumed as treatment of the subject's anaemia)' changed to 'Any iron supplementation other than investigational drug (multivitamins including iron is allowed unless it is assumed as treatment of the subject's anaemia)' and 'Chemotherapy' changed to 'Chemotherapy (except immune modulating therapy for standard IBD treatment)'. • Inclusion of baseline body weight and baseline Hb as additional covariates in the sensitivity analysis of the primary endpoint. • Change of safety reference document for iron isomaltoside from the Monofer® Investigator's Brochure to the Monofer® SmPC since treatment with iron isomaltoside in this trial was within the label and the same SmPC is approved in all the participating countries.
15 July 2019	• Omission of iFGF23 from the eligibility laboratory assessments at screening as iFGF23 was not part of any inclusion or exclusion criteria or stratification. • Deletion of the secondary safety objective 'To compare the effects of iron isomaltoside and ferric carboxymaltose treatment in subjects with IDA due to IBD on proportion of subjects with hypophosphatemia at the last visit' since this objective is already covered in the primary objective. • In the primary endpoint, the definition of hypophosphatemia was further detailed and the unit used for the time period was changed from days to weeks. • In the secondary safety endpoints, 's phosphate < 1.0 mg/dL' was changed to 's phosphate ≤ 1.0 mg/dL' in order to align with previous trials with iron isomaltoside. • Change of the endpoint 'Incidence of s-phosphate < 1.0 mg/dL at any time from baseline to day 35' to 'Incidence of s-phosphate ≤ 1.0 mg/dL at any time from baseline to week 5 and at any time from baseline to week 10' in order to align with previous trials with iron isomaltoside. • Addition of the secondary safety endpoints, 'Incidence of hypophosphatemia at day 1 and weeks 1, 2, 5, 6, 7, and 10' and 'Incidence of s phosphate ≤ 1.0 mg/dL at day 1 and weeks 1, 2, 5, 6, 7, and 10', including description of statistical analyses of these endpoints, in order to align with previous trials with iron isomaltoside. • Clarification that the secondary safety endpoint on fractional phosphate urinary excretion was derived as change from baseline to day 1 and weeks 1, 2, 5, 6, 7, and 10. • Change and expansion of the statistical analysis of AEs from 'Number of subjects who experience an ADR including SUSARs will be compared between treatment groups' to 'The incidence of TEAEs, SAEs, ADRs including SUSARs as well as SARs will be compared between treatment groups' in order to align with previous trials with iron isomaltoside.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported