Clinical trial results:
A prospective, non-controlled, safety trial of intravenous iron isomaltoside 1000 (Monofer®) administered by a high dosing regimen in subjects with inflammatory bowel disease (PROMISE)

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

Summary

EudraCT number	2011-003121-94
Trial protocol	DK SE NL
Global end of trial date	27 November 2014

Results information

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

Trial information

Trial identification

Sponsor protocol code	P-Monofer-IBD-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01599702
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	27 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 November 2014
Global end of trial reached?	Yes
Global end of trial date	27 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the safety of a high IV iron dosing regimen of iron isomaltoside 1000 in subjects with IDA secondary to IBD.

Protection of trial subjects:

The protocol and amendments were approved by local ethics committees/Institutional Review Boards and competent authorities. The trial was conducted in accordance with good clinical practice and the Declaration of Helsinki. Informed consent was obtained in writing prior to any trial-related activities.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 July 2012
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	Netherlands: 5
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Denmark: 12
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	19
From 65 to 84 years	2

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were screened in the period 24 July 2012 to 4 September 2014. The trial took place at 6 sites: 3 sites in Sweden (no subjects were enrolled at 2 of these sites), 2 in Denmark, and 1 in Netherlands.

Pre-assignment

Screening details:

Subjects who were ≥18 years of age, diagnosed with IBD in all activity stages, and with a Hb level of <12 g/dL for women and Hb <13 g/dL for men were eligible to participate. Subjects with CRP above the upper limit of normal (ULN) had to have a ferritin level <100 µg/L, whereas subjects with a CRP ≤ULN had to have a ferritin level <30 µg/L.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A1, 1500 mg iron isomaltoside 1000

Arm description:

The single dose of 1500 mg Iron isomaltoside 1000 was administered at baseline in the 1500 mg group. Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.

Arm type	Experimental
Investigational medicinal product name	Iron isomaltoside 1000
Investigational medicinal product code	ATC code: B03AC
Other name	Monofer, Monover, Monofar, Monoferro
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Based upon the Hb level and body weight, the subjects were divided into 4 treatment groups:
Group A1, women: 10 ≤ Hb < 12 g/dL and men: 11 ≤ Hb < 13 g/dL with a body weight <70 kg received 1500 mg iron.
Group A2, women: 10 ≤ Hb < 12 g/dL and men: 11 ≤ Hb < 13 g/dL with a body weight ≥70 kg received 2000 mg iron.
Group B1, women: Hb < 10 g/dL and men: Hb < 11 g/dL with a body weight <70 kg received 2500 mg iron.
Group B2, women: Hb < 10 g/dL and men: Hb < 11 g/dL with a body weight ≥70 kg received 3000 mg iron.
The single dose of 1500 mg was administered at baseline, whereas the cumulative doses of 2000 mg were administered in 1 or 2 doses, and the cumulative doses of 2500 mg and 3000 mg were administered in 2 doses. All administrations were diluted in 100 mL normal saline and administered by infusion over app 15 min.
Iron isomaltoside 1000 is available as a dark brown, non-transparent aqueous solution for injection/infusion containing 100 mg iron/mL with pH between 5.0 and 7.0.

Arm title	Group A2, 2000 mg iron isomaltoside 1000

Arm description:

The cumulative doses of 2000 mg were administered in 1 or 2 doses (subjects enrolled according to the original protocol received 2000 mg in one dose, and subjects enrolled according to the amended protocol received 2000 mg in two doses).
Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.

Arm type	Experimental

Investigational medicinal product name	Iron isomaltoside 1000
Investigational medicinal product code	ATC code: B03AC
Other name	Monofer, Monover, Monofar, Monoferro
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Based upon the Hb level and body weight, the subjects were divided into 4 treatment groups:
Group A1, women: 10 ≤ Hb < 12 g/dL and men: 11 ≤ Hb < 13 g/dL with a body weight <70 kg received 1500 mg iron.
Group A2, women: 10 ≤ Hb < 12 g/dL and men: 11 ≤ Hb < 13 g/dL with a body weight ≥70 kg received 2000 mg iron.
Group B1, women: Hb < 10 g/dL and men: Hb < 11 g/dL with a body weight <70 kg received 2500 mg iron.
Group B2, women: Hb < 10 g/dL and men: Hb < 11 g/dL with a body weight ≥70 kg received 3000 mg iron.
The single dose of 1500 mg was administered at baseline, whereas the cumulative doses of 2000 mg were administered in 1 or 2 doses, and the cumulative doses of 2500 mg and 3000 mg were administered in 2 doses. All administrations were diluted in 100 mL normal saline and administered by infusion over app 15 min.
Iron isomaltoside 1000 is available as a dark brown, non-transparent aqueous solution for injection/infusion containing 100 mg iron/mL with pH between 5.0 and 7.0.

Arm title	Group B1, 2500 mg iron isomaltoside 1000

Arm description:

The cumulative dose of 2500 mg were administered in 2 doses. Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.

Arm type	Experimental
Investigational medicinal product name	Iron isomaltoside 1000
Investigational medicinal product code	ATC code: B03AC
Other name	Monofer, Monover, Monofar, Monoferro
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Based upon the Hb level and body weight, the subjects were divided into 4 treatment groups:
Group A1, women: 10 ≤ Hb < 12 g/dL and men: 11 ≤ Hb < 13 g/dL with a body weight <70 kg received 1500 mg iron.
Group A2, women: 10 ≤ Hb < 12 g/dL and men: 11 ≤ Hb < 13 g/dL with a body weight ≥70 kg received 2000 mg iron.
Group B1, women: Hb < 10 g/dL and men: Hb < 11 g/dL with a body weight <70 kg received 2500 mg iron.
Group B2, women: Hb < 10 g/dL and men: Hb < 11 g/dL with a body weight ≥70 kg received 3000 mg iron.
The single dose of 1500 mg was administered at baseline, whereas the cumulative doses of 2000 mg were administered in 1 or 2 doses, and the cumulative doses of 2500 mg and 3000 mg were administered in 2 doses. All administrations were diluted in 100 mL normal saline and administered by infusion over app 15 min.
Iron isomaltoside 1000 is available as a dark brown, non-transparent aqueous solution for injection/infusion containing 100 mg iron/mL with pH between 5.0 and 7.0.

Arm title	Group B2, 3000 mg iron isomaltoside 1000

Arm description:

The cumulative dose of 3000 mg were administered in 2 doses. Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.

Arm type	Experimental
Investigational medicinal product name	Iron isomaltoside 1000
Investigational medicinal product code	ATC code: B03AC
Other name	Monofer, Monover, Monofar, Monoferro
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Based upon the Hb level and body weight, the subjects were divided into 4 treatment groups:
Group A1, women: 10 ≤ Hb < 12 g/dL and men: 11 ≤ Hb < 13 g/dL with a body weight <70 kg

received 1500 mg iron.
Group A2, women: 10 ≤ Hb < 12 g/dL and men: 11 ≤ Hb < 13 g/dL with a body weight ≥70 kg received 2000 mg iron.
Group B1, women: Hb < 10 g/dL and men: Hb < 11 g/dL with a body weight <70 kg received 2500 mg iron.
Group B2, women: Hb < 10 g/dL and men: Hb < 11 g/dL with a body weight ≥70 kg received 3000 mg iron.
The single dose of 1500 mg was administered at baseline, whereas the cumulative doses of 2000 mg were administered in 1 or 2 doses, and the cumulative doses of 2500 mg and 3000 mg were administered in 2 doses. All administrations were diluted in 100 mL normal saline and administered by infusion over app 15 min.
Iron isomaltoside 1000 is available as a dark brown, non-transparent aqueous solution for injection/infusion containing 100 mg iron/mL with pH between 5.0 and 7.0.

Number of subjects in period 1	Group A1, 1500 mg iron isomaltoside 1000	Group A2, 2000 mg iron isomaltoside 1000	Group B1, 2500 mg iron isomaltoside 1000
Started	7	8	4
Completed	6	8	4
Not completed	1	0	0
Protocol deviation	1	-	-

Number of subjects in period 1	Group B2, 3000 mg iron isomaltoside 1000
Started	2
Completed	2
Not completed	0
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Group A1, 1500 mg iron isomaltoside 1000
Reporting group description:	
The single dose of 1500 mg Iron isomaltoside 1000 was administered at baseline in the 1500 mg group. Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.	
Reporting group title	Group A2, 2000 mg iron isomaltoside 1000
Reporting group description:	
The cumulative doses of 2000 mg were administered in 1 or 2 doses (subjects enrolled according to the original protocol received 2000 mg in one dose, and subjects enrolled according to the amended protocol received 2000 mg in two doses). Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.	
Reporting group title	Group B1, 2500 mg iron isomaltoside 1000
Reporting group description:	
The cumulative dose of 2500 mg were administered in 2 doses. Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.	
Reporting group title	Group B2, 3000 mg iron isomaltoside 1000
Reporting group description:	
The cumulative dose of 3000 mg were administered in 2 doses. Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.	

Reporting group values	Group A1, 1500 mg iron isomaltoside 1000	Group A2, 2000 mg iron isomaltoside 1000	Group B1, 2500 mg iron isomaltoside 1000
Number of subjects	7	8	4
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age is calculated by subtracting the screening visit date with the birth date.			
Units: years arithmetic mean standard deviation	 33.3 ± 13.9	 51 ± 11.7	 47.3 ± 19.6
Gender categorical Units: Subjects			
Female Male	7 0	6 2	3 1

Reporting group values	Group B2, 3000 mg iron isomaltoside 1000	Total	

Number of subjects	2	21	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age is calculated by subtracting the screening visit date with the birth date.			
Units: years			
arithmetic mean	33.5		
standard deviation	± 2.1	-	
Gender categorical Units: Subjects			
Female	0	16	
Male	2	5	

Subject analysis sets

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population (N=21) included all subjects who were randomised and received at least one dose of the trial drug.

Reporting group values	Safety analysis set		
Number of subjects	21		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age is calculated by subtracting the screening visit date with the birth date.			
Units: years			
arithmetic mean	42.7		
standard deviation	± 15.3		

Gender categorical Units: Subjects			
Female	16		
Male	5		

End points

End points reporting groups

Reporting group title	Group A1, 1500 mg iron isomaltoside 1000

Reporting group description:

The single dose of 1500 mg Iron isomaltoside 1000 was administered at baseline in the 1500 mg group. Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.

Reporting group title	Group A2, 2000 mg iron isomaltoside 1000

Reporting group description:

The cumulative doses of 2000 mg were administered in 1 or 2 doses (subjects enrolled according to the original protocol received 2000 mg in one dose, and subjects enrolled according to the amended protocol received 2000 mg in two doses).
Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.

Reporting group title	Group B1, 2500 mg iron isomaltoside 1000

Reporting group description:

The cumulative dose of 2500 mg were administered in 2 doses. Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.

Reporting group title	Group B2, 3000 mg iron isomaltoside 1000

Reporting group description:

The cumulative dose of 3000 mg were administered in 2 doses. Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population (N=21) included all subjects who were randomised and received at least one dose of the trial drug.

Primary: Type and incidence of adverse drug reactions

End point title	Type and incidence of adverse drug reactions[1]

End point description:

Type and incidence of adverse drug reaction.

The analysis was performed on the safety population.

End point type	Primary

End point timeframe:

The endpoint covered the complete trial period.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoint is type and incidence of adverse drug reactions since this was a safety trial. The endpoint is described purely descriptively and no statistical analysis was performed.

End point values	Group A1, 1500 mg iron isomaltoside 1000	Group A2, 2000 mg iron isomaltoside 1000	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	4	2
Units: Number of adverse drug reactions	4	3	0	2

Statistical analyses

No statistical analyses for this end point

Secondary: Change in haemoglobin from baseline to week 1

End point title	Change in haemoglobin from baseline to week 1

End point description:

Change in haemoglobin from baseline to week 1.

Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in haemoglobin from baseline to week 1.

End point values	Group A1, 1500 mg iron isomaltoside 1000	Group A2, 2000 mg iron isomaltoside 1000	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	8	4	2
Units: g/dL				
median (full range (min-max))	0.8 (-0.1 to 1)	0.55 (-0.6 to 1.5)	1.3 (1.1 to 1.4)	1.3 (1.1 to 1.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in haemoglobin from baseline to week 4

End point title	Change in haemoglobin from baseline to week 4

End point description:

Change in haemoglobin from baseline to week 4.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in haemoglobin from baseline to week 4.

End point values	Group A1, 1500 mg iron isomaltoside 1000	Group A2, 2000 mg iron isomaltoside 1000	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	7	4	1
Units: g/dL				
median (full range (min-max))	2.05 (0.9 to 2.9)	1.7 (0.6 to 3.5)	3.15 (0.3 to 3.9)	4 (4 to 4)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in haemoglobin from baseline to week 8

End point title	Change in haemoglobin from baseline to week 8

End point description:

Change in haemoglobin from baseline to week 8.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in haemoglobin from baseline to week 8.

End point values	Group A1, 1500 mg iron isomaltoside 1000	Group A2, 2000 mg iron isomaltoside 1000	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	8	4	2
Units: g/dL				
median (full range (min-max))	2.35 (0.5 to 3.8)	2.65 (1 to 4.2)	2.5 (-0.1 to 4.1)	3.9 (3.2 to 4.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in haemoglobin from baseline to week 9

End point title	Change in haemoglobin from baseline to week 9[2]

End point description:

Change in haemoglobin from baseline to week 9.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in haemoglobin from baseline to week 9.

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Patients in group A1 and A2 was only enrolled for 8 weeks, whereas patients in group B1 and B2 were enrolled in 16 weeks. Therefore, no data is available for patients in group A1 and A2 after week 8.

End point values	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: g/dL				
median (full range (min-max))	2.25 (1.4 to 4)	4.45 (4.1 to 4.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in haemoglobin from baseline to week 12

End point title	Change in haemoglobin from baseline to week 12[3]

End point description:

Change in haemoglobin from baseline to week 12.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in haemoglobin from baseline to week 12.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Patients in group A1 and A2 was only enrolled for 8 weeks, whereas patients in group B1 and B2 were enrolled in 16 weeks. Therefore, no data is available for patients in group A1 and A2 after week 8.

End point values	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: g/dL				
median (full range (min-max))	3.1 (0.9 to 4.3)	5 (4.8 to 5.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in haemoglobin from baseline to week 16

End point title	Change in haemoglobin from baseline to week 16[4]

End point description:

Change in haemoglobin from baseline to week 16.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in haemoglobin from baseline to week 16.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Patients in group A1 and A2 was only enrolled for 8 weeks, whereas patients in group B1 and B2 were enrolled in 16 weeks. Therefore, no data is available for patients in group A1 and A2 after week 8.

End point values	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: g/dL				
median (full range (min-max))	2.45 (-0.7 to 4.4)	4.95 (4.9 to 5)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Change in s-ferritin from baseline to week 1.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to week 1.

End point values	Group A1, 1500 mg iron isomaltoside 1000	Group A2, 2000 mg iron isomaltoside 1000	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	8	4	2
Units: ug/L				
median (full range (min-max))	723.5 (524 to 1432)	732.5 (526 to 1194)	752 (335 to 1106)	428 (401 to 455)

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Change in s-ferritin from baseline to week 4.

Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to week 4.

End point values	Group A1, 1500 mg iron isomaltoside 1000	Group A2, 2000 mg iron isomaltoside 1000	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	8	4	1
Units: ug/L				
median (full range (min-max))	180 (96 to 700)	336 (149 to 483)	154 (64 to 357)	45 (45 to 45)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in s-ferritin from baseline to week 8

End point title	Change in s-ferritin from baseline to week 8

End point description:

Change in s-ferritin from baseline to week 8.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to week 8.

End point values	Group A1, 1500 mg iron isomaltoside 1000	Group A2, 2000 mg iron isomaltoside 1000	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	8	4	2
Units: ug/L				
median (full range (min-max))	142 (59 to 458)	225 (83 to 417)	65 (6 to 272)	55.5 (10 to 101)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in s-ferritin from baseline to week 9.

End point title	Change in s-ferritin from baseline to week 9.[5]

End point description:

Change in s-ferritin from baseline to week 9.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to week 9.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Patients in group A1 and A2 was only enrolled for 8 weeks, whereas patients in group B1 and B2 were enrolled in 16 weeks. Therefore, no data is available for patients in group A1 and A2 after week 8.

End point values	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: ug/L				
median (full range (min-max))	259 (162 to 1753)	428 (372 to 484)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change in s-ferritin from baseline to week 12[6]

End point description:

Change in s-ferritin from baseline to week 12.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to week 12.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Patients in group A1 and A2 was only enrolled for 8 weeks, whereas patients in group B1 and B2 were enrolled in 16 weeks. Therefore, no data is available for patients in group A1 and A2 after week 8.

End point values	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: ug/L				
median (full range (min-max))	96 (58 to 765)	182 (89 to 275)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in s-ferritin from baseline to week 16

End point title	Change in s-ferritin from baseline to week 16[7]

End point description:

Change in s-ferritin from baseline to week 16.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in s-ferritin from baseline to week 16.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Patients in group A1 and A2 was only enrolled for 8 weeks, whereas patients in group B1 and B2 were enrolled in 16 weeks. Therefore, no data is available for patients in group A1 and A2 after week 8.

End point values	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: ug/L				
median (full range (min-max))	33 (5 to 615)	178.5 (19 to 338)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in transferrin saturation from baseline to week 1

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

End point description:

Change in transferrin saturation from baseline to week 1.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to week 1.

End point values	Group A1, 1500 mg iron isomaltoside 1000	Group A2, 2000 mg iron isomaltoside 1000	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	8	4	2
Units: percentage				
median (full range (min-max))	26 (11 to 54)	19.5 (11 to 39)	26 (6 to 34)	13.5 (11 to 16)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in transferrin saturation from baseline to week 4.

End point title	Change in transferrin saturation from baseline to week 4.

End point description:

Change in transferrin saturation from baseline to week 4.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to week 4.

End point values	Group A1, 1500 mg iron isomaltoside 1000	Group A2, 2000 mg iron isomaltoside 1000	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	8	4	1
Units: percentage				
median (full range (min-max))	23.5 (12 to 29)	16.5 (10 to 27)	13 (2 to 21)	9 (9 to 9)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in transferrin saturation from baseline to week 8

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

End point description:

Change in transferrin saturation from baseline to week 8.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to week 8.

End point values	Group A1, 1500 mg iron isomaltoside 1000	Group A2, 2000 mg iron isomaltoside 1000	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	8	4	2
Units: percentage				
median (full range (min-max))	32 (15 to 38)	19 (2 to 23)	4.5 (-1 to 11)	13 (9 to 17)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in transferrin saturation from baseline to week 9

End point title	Change in transferrin saturation from baseline to week 9[8]

End point description:

Change in transferrin saturation from baseline to week 9.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to week 9.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Patients in group A1 and A2 was only enrolled for 8 weeks, whereas patients in group B1 and B2 were enrolled in 16 weeks. Therefore, no data is available for patients in group A1 and A2 after week 8.

End point values	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: percentage				
median (full range (min-max))	10 (4 to 29)	33 (14 to 52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in transferrin saturation from baseline to week 12

End point title	Change in transferrin saturation from baseline to week 12[9]

End point description:

Change in transferrin saturation from baseline to week 12.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to week 12.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Patients in group A1 and A2 was only enrolled for 8 weeks, whereas patients in group B1 and B2 were enrolled in 16 weeks. Therefore, no data is available for patients in group A1 and A2 after week 8.

End point values	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: percentage				
median (full range (min-max))	10.5 (3 to 24)	25 (23 to 27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in transferrin saturation from baseline to week 16

End point title	Change in transferrin saturation from baseline to week 16[10]

End point description:

Change in transferrin saturation from baseline to week 16.
Analysis performed on the safety analysis set.

End point type	Secondary

End point timeframe:

Change in transferrin saturation from baseline to week 16.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Patients in group A1 and A2 was only enrolled for 8 weeks, whereas patients in group B1 and B2 were enrolled in 16 weeks. Therefore, no data is available for patients in group A1 and A2 after week 8.

End point values	Group B1, 2500 mg iron isomaltoside 1000	Group B2, 3000 mg iron isomaltoside 1000		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: percentage				
median (full range (min-max))	9 (2 to 19)	13.5 (6 to 21)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time a subject had signed the ICF and until he/she had completed the trial, all AEs/SAEs were collected in the CRF.

Adverse event reporting additional description:

All AEs classified as serious and/or related to the study drug were followed by the principle investigator (PI) until the subject had recovered, recovered with sequelae, or died, and until all queries related to the AEs had been resolved. All other AEs were followed by the PI until the subject had recovered or until EOS whichever came first.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Group A1, 1500 mg iron isomaltoside 1000

Reporting group description:

The single dose of 1500 mg Iron isomaltoside 1000 was administered at baseline in the 1500 mg group. Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.

Reporting group title	Group A2, 2000 mg iron isomaltoside 1000

Reporting group description:

The cumulative doses of 2000 mg were administered in 1 or 2 doses (subjects enrolled according to the original protocol received 2000 mg in one dose, and subjects enrolled according to the amended protocol received 2000 mg in two doses).
Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.

Reporting group title	Group B1, 2500 mg iron isomaltoside 1000

Reporting group description:

The cumulative dose of 2500 mg were administered in 2 doses. Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.

Reporting group title	Group B2, 3000 mg iron isomaltoside 1000

Reporting group description:

The cumulative dose of 3000 mg were administered in 2 doses. Iron isomaltoside 1000 were diluted in 100 mL normal saline (0.9% sodium chloride) and administered by infusion over approximately 15 min.

Serious adverse events	Group A1, 1500 mg iron isomaltoside 1000	Group A2, 2000 mg iron isomaltoside 1000	Group B1, 2500 mg iron isomaltoside 1000
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Group B2, 3000 mg iron isomaltoside 1000		
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 2 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Group A1, 1500 mg iron isomaltoside 1000	Group A2, 2000 mg iron isomaltoside 1000	Group B1, 2500 mg iron isomaltoside 1000
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	6 / 8 (75.00%)	3 / 4 (75.00%)
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Seasonal allergy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Investigations			
Faecal calprotectin increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Haematocrit decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Mean cell haemoglobin concentration decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Mean cell volume increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Red blood cell count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Transferrin decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Vitamin D decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Eye allergy			

subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Aphthous stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Crohn's disease			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Defaecation urgency			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Irritable bowel syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Renal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Bone pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 8 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Erysipelas			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Non-serious adverse events	Group B2, 3000 mg iron isomaltoside 1000		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Chills			

subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Seasonal allergy			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Investigations			
Faecal calprotectin increased			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Haematocrit decreased			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Mean cell haemoglobin concentration decreased			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Mean cell volume increased			

subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Red blood cell count decreased subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Transferrin decreased subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Vitamin D decreased subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Eye disorders Eye allergy subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 2		
Gastrointestinal disorders Dyspepsia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Abdominal pain subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Aphthous stomatitis subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Constipation			

subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Crohn's disease			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Defaecation urgency			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Irritable bowel syndrome			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Renal pain			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Bone pain			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Neck pain			

subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Erysipelas subjects affected / exposed occurrences (all)	 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 January 2013	• Change in address of the biostatistician • Enrolment period was increased from 6 months to 18 months • The maximum single dosing of iron isomaltoside 1000 was reduced from 2000 mg to 1500 mg • Addition of a secondary safety endpoint "number of AEs of special interest (i.e. hypersensitivity reactions or hypotension at pre-specified time points in relation to administration of trial drug)" • The secondary efficacy endpoints were clarified and aligned with previous studies • Revised 6th exclusion criteria from "decompensated liver cirrhosis and/or known chronic viral hepatitis" to "decompensated liver cirrhosis or active hepatitis" • Urogenital examination was excluded from the physical examination • Added a section on re-screening of the subjects • Clarified reporting procedure of AEs • An interim analysis was planned in order to evaluate the safety and efficacy of the high dosing of iron isomaltoside 1000

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported