Clinical trial results:
A randomized, prospective, double-blind, comparative placebo-controlled study of intravenous iron isomaltoside 1000 (Monofer®) administered by infusions to iron-deficient blood donors

Summary

EudraCT number	2012-001529-28
Trial protocol	DK
Global end of trial date	23 December 2016

Results information

Result version number	v1 (current)
This version publication date	07 December 2017
First version publication date	07 December 2017

Trial information

Trial identification

Sponsor protocol code	P-Monofer-BD-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01895231
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharmacosmos A/S
Sponsor organisation address	Roervangsvej 30, Holbaek, Denmark, DK-4300
Public contact	Clinical trial disclosure desk, Pharmacosmos A/S, Pharmacosmos A/S, +45 59485935, trial@pharmacosmos.com
Scientific contact	Clinical trial disclosure desk, Pharmacosmos A/S, Pharmacosmos A/S, +45 59485935, trial@pharmacosmos.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 December 2016
Global end of trial reached?	Yes
Global end of trial date	23 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective of the study is to evaluate the effect of IV iron isomaltoside 1000 compared with placebo in first-time female donors with p-ferritin below 60 µg/L.

The safety objective of the study is to evaluate the safety of IV iron isomaltoside 1000 compared to placebo.

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	07 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 85
Worldwide total number of subjects	85
EEA total number of subjects	85

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)	85
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were screened in the period 07 June 2013 to 30 June 2016. The trial took place at one site in Denmark.

Pre-assignment

Screening details:

Women aged ≥ 18 years, who were first time blood donors and had a p-ferritin concentration < 60 ng/mL were able to participate in the trial after having signed the informed consent form.

Period 1

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

Blinding implementation details:

Randomisation, preparation, and connection of infusions were handled by personnel otherwise unrelated to the trial. Infusion bags and disposables were non-transparent. In order to ensure that, the infusion bags and all visible disposables will be wrapped in aluminium foil by the personnel unrelated to the trial. All used material will be removed by the same person without revealing the infused fluid.
The monitor performing data monitoring and site management (except IMP handling) was blinded.

Arms

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

Arm description:

1000 mg iron isomaltoside was administered as a single IV infusion.

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:

1000 mg iron isomaltoside was administered as a single IV infusion.
Iron isomaltoside is available as a dark brown, non-transparent aqueous solution for injection/infusion containing 100 mg iron/mL with pH between 5.0 and 7.0.

Arm title	Group B, placebo

Arm description:

A 100 ml 0.9 % sodium chloride solution was used as an IV placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects in the placebo group received saline (0.9 % sodium chloride) as a single dose infusion of 100 mL.

Number of subjects in period 1	Group A, iron isomaltoside	Group B, placebo
Started	43	42
Completed	40	36
Not completed	3	6
Consent withdrawn by subject	1	-
Protocol non-compliance	-	1
Could not draw blood samples due to tiny veins.	1	-
Adverse event, non-fatal	-	1
Pregnancy	-	1
Lost to follow-up	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Group A, iron isomaltoside
Reporting group description:	
1000 mg iron isomaltoside was administered as a single IV infusion.	
Reporting group title	Group B, placebo
Reporting group description:	
A 100 ml 0.9 % sodium chloride solution was used as an IV placebo.	

Reporting group values	Group A, iron isomaltoside	Group B, placebo	Total
Number of subjects	43	42	85
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 was calculated by subtracting the screening visit date with the birth date.			
Units: years			
arithmetic mean	23.2	24.9	
standard deviation	± 3.7	± 6	-
Gender categorical Units: Subjects			
Female	43	42	85
Male	0	0	0

Subject analysis sets	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all subjects who were randomized and received at least one dose of the trial drug.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS population consisted of all subjects who were randomized, received at least one dose of the trial drug, and had at least one post baseline Hb assessment.	
Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population included all subjects in the FAS who did not have any major protocol deviation.

Reporting group values	Safety population	Full analysis set	Per protocol analysis set
Number of subjects	82	80	74
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 was calculated by subtracting the screening visit date with the birth date.			
Units: years arithmetic mean standard deviation	 24.1 ± 5.1	 24.1 ± 5.1	 24.3 ± 5.3
Gender categorical Units: Subjects			
Female Male	82 0	80 0	74 0

End points

End points reporting groups

Reporting group title	Group A, iron isomaltoside
Reporting group description:	
1000 mg iron isomaltoside was administered as a single IV infusion.	
Reporting group title	Group B, placebo
Reporting group description:	
A 100 ml 0.9 % sodium chloride solution was used as an IV placebo.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all subjects who were randomized and received at least one dose of the trial drug.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS population consisted of all subjects who were randomized, received at least one dose of the trial drug, and had at least one post baseline Hb assessment.	
Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population included all subjects in the FAS who did not have any major protocol deviation.	

Primary: Change in Hb concentration from baseline to right before the third blood donation, FAS

End point title	Change in Hb concentration from baseline to right before the third blood donation, FAS
End point description:	
Change in Hb concentration from baseline to right before the third blood donation. Analysis performed on the FAS.	
End point type	Primary
End point timeframe:	
Change in Hb concentration from baseline to right before the third blood donation.	

End point values	Group A, iron isomaltoside	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	34		
Units: g/dL				
arithmetic mean (standard deviation)	1.8 (± 0.777)	0.45 (± 0.883)		

Statistical analyses

Statistical analysis title	Test for superiority, ANCOVA
Statistical analysis description:	
The primary efficacy analysis was performed using an analysis of covariance (ANCOVA) with treatment	

as factor and baseline value as covariate.

Comparison groups	Group A, iron isomaltoside v Group B, placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.2527
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8979
upper limit	1.6076
Variability estimate	Standard error of the mean
Dispersion value	0.1782

Primary: Change in Hb concentration from baseline to right before the third blood donation, PP

End point title	Change in Hb concentration from baseline to right before the third blood donation, PP

End point description:

Change in Hb concentration from baseline to right before the third blood donation.
Analysis performed on the PP analysis set.

End point type	Primary

End point timeframe:

Change in Hb concentration from baseline to right before the third blood donation.

End point values	Group A, iron isomaltoside	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	33		
Units: g/dL				
arithmetic mean (standard deviation)	1.86 (± 0.74)	0.44 (± 0.896)		

Statistical analyses

Statistical analysis title	Test for superiority, ANCOVA

Statistical analysis description:

The primary efficacy analysis was performed using an analysis of covariance (ANCOVA) with treatment.

Comparison groups	Group A, iron isomaltoside v Group B, placebo

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.3054
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9357
upper limit	1.6751
Variability estimate	Standard error of the mean
Dispersion value	0.1854

Secondary: Change in Hb concentrations from baseline to right before second donation

End point title	Change in Hb concentrations from baseline to right before second donation

End point description:

Change in Hb concentrations from baseline to right before second donation.
Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in Hb concentrations from baseline to right before second donation.

End point values	Group A, iron isomaltoside	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: g/dL				
arithmetic mean (standard deviation)	1.72 (± 0.748)	1.35 (± 0.801)		

Statistical analyses

Statistical analysis title	Test for superiority, ANCOVA

Statistical analysis description:

The secondary efficacy analysis was performed using an analysis of covariance (ANCOVA) with treatment.

Comparison groups	Group A, iron isomaltoside v Group B, placebo

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0327
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.3538
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.678
Variability estimate	Standard error of the mean
Dispersion value	0.163

Secondary: Change in p-ferritin concentrations from baseline to 12 weeks after first blood donation

End point title	Change in p-ferritin concentrations from baseline to 12 weeks after first blood donation

End point description:

Change in p-ferritin concentrations from baseline to 12 weeks after first blood donation.
Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in p-ferritin concentrations from baseline to 12 weeks after first blood donation.

End point values	Group A, iron isomaltoside	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	36		
Units: ng/mL				
arithmetic mean (standard deviation)	149.5 (± 69.75)	9.1 (± 10.51)		

Statistical analyses

Statistical analysis title	Test for superiority, ANCOVA

Statistical analysis description:

The secondary efficacy analysis was performed using an analysis of covariance (ANCOVA) with treatment.

Comparison groups	Group A, iron isomaltoside v Group B, placebo

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	135.0135
Confidence interval	
level	95 %
sides	2-sided
lower limit	112.135
upper limit	157.892
Variability estimate	Standard error of the mean
Dispersion value	11.477

Secondary: Change in p-ferritin concentrations from baseline to 12 weeks after second blood donation

End point title	Change in p-ferritin concentrations from baseline to 12 weeks after second blood donation

End point description:

Change in p-ferritin concentrations from baseline to 12 weeks after second blood donation.
Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in p-ferritin concentrations from baseline to 12 weeks after second blood donation.

End point values	Group A, iron isomaltoside	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	33		
Units: ng/mL				
arithmetic mean (standard deviation)	62.9 (± 31.82)	1.2 (± 9.47)		

Statistical analyses

Statistical analysis title	Test for superiority, ANCOVA

Statistical analysis description:

The secondary efficacy analysis was performed using an analysis of covariance (ANCOVA) with treatment.

Comparison groups	Group A, iron isomaltoside v Group B, placebo

Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	59.7535
Confidence interval	
level	95 %
sides	2-sided
lower limit	48.177
upper limit	71.33
Variability estimate	Standard error of the mean
Dispersion value	5.805

Secondary: Change in transferrin saturation concentrations from baseline to 12 weeks after first blood donation

End point title	Change in transferrin saturation concentrations from baseline to 12 weeks after first blood donation

End point description:

Change in transferrin saturation concentrations from baseline to 12 weeks after first blood donation. Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in transferrin saturation concentrations from baseline to 12 weeks after first blood donation.

End point values	Group A, iron isomaltoside	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	36		
Units: Percentage				
arithmetic mean (standard deviation)	15.821 (± 11.9822)	6.75 (± 11.2868)		

Statistical analyses

Statistical analysis title	Test for superiority, ANCOVA

Statistical analysis description:

The secondary efficacy analysis was performed using an analysis of covariance (ANCOVA) with treatment.

Comparison groups	Group A, iron isomaltoside v Group B, placebo

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	9.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.821
upper limit	14.519
Variability estimate	Standard error of the mean
Dispersion value	2.432

Secondary: Change in transferrin saturation concentrations from baseline to 12 weeks after second blood donation

End point title	Change in transferrin saturation concentrations from baseline to 12 weeks after second blood donation

End point description:

Change in transferrin saturation concentrations from baseline to 12 weeks after second blood donation. Analysis performed on the FAS.

End point type	Secondary

End point timeframe:

Change in transferrin saturation concentrations from baseline to 12 weeks after second blood donation.

End point values	Group A, iron isomaltoside	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	33		
Units: Percentage				
arithmetic mean (standard deviation)	12.625 (± 9.6548)	2.848 (± 13.0411)		

Statistical analyses

Statistical analysis title	Test for superiority, ANCOVA

Statistical analysis description:

The secondary efficacy analysis was performed using an analysis of covariance (ANCOVA) with treatment.

Comparison groups	Group A, iron isomaltoside v Group B, placebo

Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	10.7474
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.869
upper limit	15.626
Variability estimate	Standard error of the mean
Dispersion value	2.446

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time a subject had signed the informed consent form and until he/she had completed the study, all AEs/SAEs were reported in the CRF.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Group A, iron isomaltoside

Reporting group description:

1000 mg iron isomaltoside was administered as a single IV infusion.

Reporting group title	Group B, placebo

Reporting group description:

A 100 ml 0.9 % sodium chloride solution will be used as an IV placebo.

Serious adverse events	Group A, iron isomaltoside	Group B, placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 41 (4.88%)	1 / 41 (2.44%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 41 (2.44%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group A, iron isomaltoside	Group B, placebo	
Total subjects affected by non-serious adverse events subjects affected / exposed	28 / 41 (68.29%)	31 / 41 (75.61%)	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2	4 / 41 (9.76%) 4	
Headache subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 3	4 / 41 (9.76%) 4	
Migraine subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	3 / 41 (7.32%) 3	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	5 / 41 (12.20%) 6	
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	3 / 41 (7.32%) 3	
Infections and infestations Cystitis subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3	0 / 41 (0.00%) 0	
Influenza subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3	2 / 41 (4.88%) 2	
Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 41 (17.07%) 8	7 / 41 (17.07%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2014	• Change of inclusion criterion 3 from 'P-ferritin < 30 ng/mL' to 'P-ferritin < 60 ng/mL' • Change of inclusion criterion 8 from a specific list of contraceptives required to the more general term 'adequate contraception (e.g. intrauterine devices, hormonal contraceptives, or double barrier method)' • Specification that pre-planned procedures and pre-existing conditions that had not worsened were to be recorded on the medical history pages of the CRF • Change from the current SmPC to the current Investigator's Brochure for assessing expectedness of AEs • Specification that it was the responsibility of Pharmacosmos to evaluate the SARs for expectedness • Specification of the time period for reporting of AEs (from the time a subject had signed the ICF and until she had completed the trial) • Change of reporting of SAEs (to be reported to Drug Safety, Pharmacosmos, instead of to Max Neeman International) • The sentence stating that the trial would have a review committee for regular review of safety data was deleted
05 August 2015	• The requirement of a maximum of 40 subjects to participate in the exercise test at visit 2 and visit 2a was removed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported