Clinical trial results:
A randomised, prospective, double-blind, comparative placebo-controlled study of intrave-nous iron isomaltoside 1000 (Monofer®) administered by infusions to non-anaemic patients undergoing elective or sub-acute CABG, valve replacement, or a combination thereof

Summary

EudraCT number	2010-023788-16
Trial protocol	DK
Global end of trial date	02 August 2013

Results information

Result version number	v2 (current)
This version publication date	07 April 2016
First version publication date	16 July 2015
Version creation reason	• Correction of full data set Some incorrect data was discovered during the review process.

Trial information

Trial identification

Sponsor protocol code	P-Monofer-CABG-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01563367
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	02 August 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 August 2013
Global end of trial reached?	Yes
Global end of trial date	02 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective of the study was to demonstrate that IV iron isomaltoside 1000 is superior compared to placebo in leading to a less decrease in the Hb level in non-anaemic patients undergoing cardiac surgery.

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	13 December 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	Denmark: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	21
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were screened in the period 13 December 2012 to 01 July 2013. The trial took place at one site in Denmark.

Pre-assignment

Screening details:

Subjects ≥ 18 years of age undergoing elective or sub-acute CABG, valve replacement, or a combination thereof, with a Hb ≥ 12.0 g/dL (7.45 mmol/L) for women and a Hb ≥ 13.0 g/dL (8.1 mmol/L) for men, and who were willing to provide written informed consent were considered eligible to participate in the trial.

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	Investigator, Subject

Blinding implementation details:

The study drug was administered while the patient was in anaesthesia in order to keep the patient blinded. The randomisation, preparation, connection of infusions, and removal of used infusion material was handled by personnel otherwise unrelated to the study. The infusion bags of iron isomaltoside 1000 and placebo were of similar sizes and brand.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A, iron isomaltoside 1000

Arm description:

Subjects in the iron isomaltoside 1000 group received iron isomaltoside 1000 as a single dose infusion of 1000 mg over 15 min with a maximum single dose of 20 mg/kg.

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:

Subjects in the iron isomaltoside 1000 group received iron isomaltoside 1000 as a single dose infusion of 1000 mg over 15 min with a maximum single dose of 20 mg/kg.
Iron isomaltoside 1000 is available as a dark brown, non-transparent aqueous solution for injection/infusion containing 100 mg iron/mL with pH between 5.0 and 7.0.

Arm title	Group B, placebo

Arm description:

Subjects in the placebo group received saline (Natriumklorid 9 mg/mL, Fresenius Kabi, Copenhagen, Denmark) as a single dose infusion of 100 mL over 15 min.

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

Dosage and administration details:

Subjects in the placebo group received saline (Natriumklorid 9 mg/mL, Fresenius Kabi, Copenhagen, Denmark) as a single dose infusion of 100 mL over 15 min

Number of subjects in period 1	Group A, iron isomaltoside 1000	Group B, placebo
Started	30	30
Completed	26	25
Not completed	4	5
Consent withdrawn by subject	1	-
Non-compliance	3	5

Baseline characteristics

Reporting groups	
Reporting group title	Group A, iron isomaltoside 1000
Reporting group description:	
Subjects in the iron isomaltoside 1000 group received iron isomaltoside 1000 as a single dose infusion of 1000 mg over 15 min with a maximum single dose of 20 mg/kg.	
Reporting group title	Group B, placebo
Reporting group description:	
Subjects in the placebo group received saline (Natriumklorid 9 mg/mL, Fresenius Kabi, Copenhagen, Denmark) as a single dose infusion of 100 mL over 15 min.	

Reporting group values	Group A, iron isomaltoside 1000	Group B, placebo	Total
Number of subjects	30	30	60
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	65.3	65	
standard deviation	± 7.9	± 10.8	-
Gender categorical			
Units: Subjects			
Female	4	4	8
Male	26	26	52

Subject analysis sets	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set consisted of all subjects who were randomized and received at least one dose of the trial drug. The subjects were included as treated.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS consisted of all subjects who were randomized into the trial, received at least one dose of the trial drug, and had a Hb assessment at visit 4. Subjects were included as randomized, regardless of which treatment they actually received.	
Subject analysis set title	Per protocol (PP) analysis set

Subject analysis set type	Per protocol

Subject analysis set description:

The PP analysis set consisted of all subjects in the FAS who did not have any major protocol deviation and had not received blood transfusion during the trial.

Reporting group values	Safety analysis set	Full analysis set (FAS)	Per protocol (PP) analysis set
Number of subjects	60	51	43
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	 65.2 ± 9.4	 66 ± 8.7	 66.5 ± 8
Gender categorical Units: Subjects			
Female Male	8 52	6 45	6 37

End points

End points reporting groups

Reporting group title	Group A, iron isomaltoside 1000

Reporting group description:

Subjects in the iron isomaltoside 1000 group received iron isomaltoside 1000 as a single dose infusion of 1000 mg over 15 min with a maximum single dose of 20 mg/kg.

Reporting group title	Group B, placebo

Reporting group description:

Subjects in the placebo group received saline (Natriumklorid 9 mg/mL, Fresenius Kabi, Copenhagen, Denmark) as a single dose infusion of 100 mL over 15 min.

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

Subject analysis set description:

The safety analysis set consisted of all subjects who were randomized and received at least one dose of the trial drug. The subjects were included as treated.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all subjects who were randomized into the trial, received at least one dose of the trial drug, and had a Hb assessment at visit 4. Subjects were included as randomized, regardless of which treatment they actually received.

Subject analysis set title	Per protocol (PP) analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The PP analysis set consisted of all subjects in the FAS who did not have any major protocol deviation and had not received blood transfusion during the trial.

Primary: Change in Hb concentrations from baseline (preoperatively – the day before surgery or the same day) to 4 weeks postoperatively, FAS

End point title	Change in Hb concentrations from baseline (preoperatively – the day before surgery or the same day) to 4 weeks postoperatively, FAS

End point description:

Change in Hb concentrations from baseline (preoperatively – the day before surgery or the same day) to 4 weeks postoperatively.

The analysis is performed on the FAS.

End point type	Primary

End point timeframe:

Change in Hb concentrations from baseline (preoperatively – the day before surgery or the same day) to 4 weeks postoperatively.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	25		
Units: g/dL				
arithmetic mean (standard deviation)	-1.61 (± 1.15)	-2.13 (± 1.09)		

Statistical analyses

Statistical analysis title	Superiority tested by ANCOVA

Statistical analysis description:

An ANCOVA model was used to compare the average change in Hb concentration from baseline to week 4.
The number of subjects may differ from the analysis population if data is missing.
The sample size calculation was based on superiority analysis, normally distributed data, Type I error = 5 %, 2-sided test, and a power of 80 %. With a sample size of 30 patients/treatment group and an assumed standard deviation of 1.50, the trial was able to detect a difference of 1.1 g/dL in change in Hb.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0124
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.7728
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	1.37
Variability estimate	Standard error of the mean
Dispersion value	0.2968

Notes:

[1] - The ANCOVA model was used to compare the average change in Hb concentration with the use of treatment, diagnostic group (a: elective CABG, b: sub-acute CABG c: valve replacement d: combination thereof) as factors and baseline Hb values as covariates.

Primary: Change in Hb concentrations from baseline (preoperatively – the day before surgery or the same day) to 4 weeks postoperatively, PP

End point title	Change in Hb concentrations from baseline (preoperatively – the day before surgery or the same day) to 4 weeks postoperatively, PP

End point description:

Change in Hb concentrations from baseline (preoperatively – the day before surgery or the same day) to 4 weeks postoperatively.

The analysis is performed on the PP analysis set.

End point type	Primary

End point timeframe:

Change in Hb concentrations from baseline (preoperatively – the day before surgery or the same day) to 4 weeks postoperatively.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	21		
Units: g/dL				
arithmetic mean (standard deviation)	-1.45 (± 1.08)	-2.16 (± 1.14)		

Statistical analyses

Statistical analysis title	Superiority tested by ANCOVA

Statistical analysis description:

An ANCOVA model was used to compare the average change in Hb concentration from baseline to week 4.
The number of subjects may differ from the analysis population if data is missing.
The sample size calculation was based on superiority analysis, normally distributed data, Type I error = 5 %, 2-sided test, and a power of 80 %. With a sample size of 30 patients/treatment group and an assumed standard deviation of 1.50, the trial was able to detect a difference of 1.1 g/dL in change in Hb.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0006
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.0825
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.67
Variability estimate	Standard error of the mean
Dispersion value	0.2896

Notes:

[2] - The ANCOVA model was used to compare the average change in Hb concentration with the use of treatment, diagnostic group (a: elective CABG, b: sub-acute CABG c: valve replacement d: combination thereof) as factors and baseline Hb values as covariates.

Secondary: Proportion of subjects that were anaemic (women < 12 g/dL and men < 13 g/dL) at day 5

End point title	Proportion of subjects that were anaemic (women < 12 g/dL and men < 13 g/dL) at day 5

End point description:

Proportion of subjects that were anaemic (women < 12 g/dL and men < 13 g/dL) at day 5.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Proportion of subjects that were anaemic (women < 12 g/dL and men < 13 g/dL) at day 5.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	25		
Units: Proportion of subjects				
Anaemic	24	25		
Non-anaemic	2	0		

Statistical analyses

Statistical analysis title	Superiority tested by Fisher Exact
Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4902
Method	Fisher exact

Secondary: Proportion of subjects that were anaemic (women < 12 g/dL and men < 13 g/dL) at week 4

End point title	Proportion of subjects that were anaemic (women < 12 g/dL and men < 13 g/dL) at week 4

End point description:

Proportion of subjects that were anaemic (women < 12 g/dL and men < 13 g/dL) at week 4.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Proportion of subjects that were anaemic (women < 12 g/dL and men < 13 g/dL) at week 4.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	25		
Units: Proportion of subjects				
Anaemic	16	23		
Non-anaemic	10	2		

Statistical analyses

Statistical analysis title	Superiority tested by Fisher Exact
Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0188
Method	Fisher exact

Secondary: Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at day 5

End point title	Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at day 5

End point description:

Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at day 5.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at day 5.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	25		
Units: Proportion of subjects				
Hb < 9.5 g/dL	7	3		
Maintain Hb (9.5 g/dL <= Hb <= 12.5 g/dL)	17	22		
Hb > 12.5 g/dL	2	0		

Statistical analyses

Statistical analysis title	Superiority tested by Fisher Exact
Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1181
Method	Fisher exact

Secondary: Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at week 4

End point title	Proportion of subjects who were able to maintain Hb between

	9.5 and 12.5 g/dL (both values included) at week 4

End point description:

Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at week 4.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Proportion of subjects who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at week 4.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	25		
Units: Proportion of subjects				
Hb < 9.5 g/dL	0	0		
Maintain Hb (9.5 g/dL <= Hb<= 12.5 g/dL)	12	19		
Hb > 12.5 g/dL	14	6		

Statistical analyses

Statistical analysis title	Superiority tested by Fisher Exact
Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0291
Method	Fisher exact

Secondary: Number of subjects in each treatment group who needed blood transfusion

End point title	Number of subjects in each treatment group who needed blood transfusion

End point description:

Number of subjects in each treatment group who needed blood transfusion.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

The endpoint covers the complete trial period.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	25		
Units: Number of subjects				
Needed blood transfusion	4	3		
Did not need blood transfusion	22	22		

Statistical analyses

Statistical analysis title	Superiority tested by Fisher Exact
Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.9999
Method	Fisher exact

Secondary: Number of transfusions administered

End point title	Number of transfusions administered

End point description:

Number of transfusions administered.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

The endpoint covers the complete trial period.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: number of blood transfusion				
arithmetic mean (standard deviation)	1.25 (± 0.5)	3 (± 2.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of serum-ferritin at day 5

End point title	Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of serum-ferritin at day 5

End point description:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of serum-ferritin at day 5.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of serum-ferritin at day 5.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: microg/L				
arithmetic mean (standard deviation)	905.88 (± 427.57)	161.62 (± 190.49)		

Statistical analyses

Statistical analysis title	Superiority tested by ANCOVA

Statistical analysis description:

An ANCOVA model was used to compare the average change in serum-ferritin concentration with the use of treatment, diagnostic group (a: elective CABG, b: sub-acute CABG c: valve replacement d: combination thereof) as factors and baseline values as covariates.

Comparison groups	Group B, placebo v Group A, iron isomaltoside 1000
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	757.5476
Confidence interval	
level	95 %
sides	2-sided
lower limit	556.474
upper limit	958.621
Variability estimate	Standard error of the mean
Dispersion value	99.7701

Secondary: Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of serum-ferritin at week 4

End point title	Change from baseline (preoperatively – the day before surgery

	or the same day) in concentrations of serum-ferritin at week 4

End point description:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of serum-ferritin at week 4.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of serum-ferritin at week 4.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	23		
Units: microg/L				
arithmetic mean (standard deviation)	398.48 (± 306.26)	-18.83 (± 124.75)		

Statistical analyses

Statistical analysis title	Superiority tested by ANCOVA

Statistical analysis description:

An ANCOVA model was used to compare the average change in serum-ferritin concentration with the use of treatment, diagnostic group (a: elective CABG, b: sub-acute CABG c: valve replacement d: combination thereof) as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	396.9232
Confidence interval	
level	95 %
sides	2-sided
lower limit	260.449
upper limit	533.397
Variability estimate	Standard error of the mean
Dispersion value	67.5767

Secondary: Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of serum-iron at day 5

End point title	Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of serum-iron at day 5

End point description:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of serum-iron at day 5.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of serum-iron at day 5.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: micromol/L				
arithmetic mean (standard deviation)	-1.38 (± 4.62)	-6.75 (± 4.19)		

Statistical analyses

Statistical analysis title	Superiority tested by ANCOVA

Statistical analysis description:

An ANCOVA model was used to compare the average change in serum-iron concentration with the use of treatment, diagnostic group (a: elective CABG, b: sub-acute CABG c: valve replacement d: combination thereof) as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.5395
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.119
upper limit	6.96
Variability estimate	Standard error of the mean
Dispersion value	0.7047

Secondary: Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of serum-iron at week 4

End point title	Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of serum-iron at week 4

End point description:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of

serum-iron at week 4.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of serum-iron at week 4.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	23		
Units: micromol/L				
arithmetic mean (standard deviation)	-0.92 (± 5.08)	-2.7 (± 4.27)		

Statistical analyses

Statistical analysis title	Superiority tested by ANCOVA

Statistical analysis description:

An ANCOVA model was used to compare the average change in serum-iron concentration with the use of treatment, diagnostic group (a: elective CABG, b: sub-acute CABG c: valve replacement d: combination thereof) as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0299
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.6376
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.269
upper limit	5.006
Variability estimate	Standard error of the mean
Dispersion value	1.1727

Secondary: Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of transferrin saturation (TSAT) at day 5

End point title	Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of transferrin saturation (TSAT) at day 5

End point description:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of transferrin saturation (TSAT) at day 5.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of transferrin saturation (TSAT) at day 5.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: percentage				
arithmetic mean (standard deviation)	4.38 (± 8.12)	-8.96 (± 6.97)		

Statistical analyses

Statistical analysis title	Superiority tested by ANCOVA

Statistical analysis description:

An ANCOVA model was used to compare the average change in transferrin saturation concentration with the use of treatment, diagnostic group (a: elective CABG, b: sub-acute CABG c: valve replacement d: combination thereof) as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	12.5977
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.697
upper limit	15.498
Variability estimate	Standard error of the mean
Dispersion value	1.4393

Secondary: Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of transferrin saturation (TSAT) at week 4

End point title	Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of transferrin saturation (TSAT) at week 4

End point description:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of transferrin saturation (TSAT) at week 4.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of transferrin saturation (TSAT) at week 4.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: percentage				
arithmetic mean (standard deviation)	0.74 (± 7.65)	-5.78 (± 7.57)		

Statistical analyses

Statistical analysis title	Superiority tested by ANCOVA

Statistical analysis description:

An ANCOVA model was used to compare the average change in transferrin saturation concentration with the use of treatment, diagnostic group (a: elective CABG, b: sub-acute CABG c: valve replacement d: combination thereof) as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	6.5229
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.649
upper limit	10.396
Variability estimate	Standard error of the mean
Dispersion value	1.9165

Secondary: Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of reticulocytes at day 5

End point title	Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of reticulocytes at day 5

End point description:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of reticulocytes at day 5.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of reticulocytes at day 5.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: 10E9/L				
arithmetic mean (standard deviation)	40.77 (± 28.89)	24.08 (± 15.1)		

Statistical analyses

Statistical analysis title	Superiority tested by ANCOVA

Statistical analysis description:

An ANCOVA model was used to compare the average change in reticulocytes concentration with the use of treatment, diagnostic group (a: elective CABG, b: sub-acute CABG c: valve replacement d: combination thereof) as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0157
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	16.1961
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.212
upper limit	29.18
Variability estimate	Standard error of the mean
Dispersion value	6.4426

Secondary: Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of reticulocytes at week 4

End point title	Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of reticulocytes at week 4

End point description:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of reticulocytes at week 4.

The analysis was performed on the FAS.

End point type	Secondary

End point timeframe:

Change from baseline (preoperatively – the day before surgery or the same day) in concentrations of reticulocytes at week 4.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: 10E9/L				
arithmetic mean (standard deviation)	16.69 (± 32.91)	20.75 (± 13.42)		

Statistical analyses

Statistical analysis title	Superiority tested by ANCOVA

Statistical analysis description:

An ANCOVA model was used to compare the average change in reticulocytes concentration with the use of treatment, diagnostic group (a: elective CABG, b: sub-acute CABG c: valve replacement d: combination thereof) as factors and baseline values as covariates.

Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3829
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.8496
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.939
upper limit	6.24
Variability estimate	Standard error of the mean
Dispersion value	5.5026

Secondary: Number of postoperative days to discharge

End point title	Number of postoperative days to discharge

End point description:

Number of postoperative days to discharge.

End point type	Secondary

End point timeframe:

This endpoint covers the complete trial period.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: days				
arithmetic mean (standard deviation)	7.56 (± 3.38)	7.96 (± 4.81)		

Statistical analyses

Statistical analysis title	Superiority tested by Wilcoxon rank sum test
Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9267
Method	Wilcoxon rank sum test

Secondary: Changes in New York Heart Association (NYHA) classification from baseline to 4 weeks postoperatively

End point title	Changes in New York Heart Association (NYHA) classification from baseline to 4 weeks postoperatively

End point description:

Changes in New York Heart Association (NYHA) classification from baseline to 4 weeks postoperatively.

End point type	Secondary

End point timeframe:

Changes in New York Heart Association (NYHA) classification from baseline to 4 weeks postoperatively.

End point values	Group A, iron isomaltoside 1000	Group B, placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	12		
Units: NYHA class				
Increase in NYHA class	0	0		
Unchanged NYHA class	6	6		
Decrease in NYHA class	7	6		

Statistical analyses

Statistical analysis title	Unchanged NYHA class
Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8475
Method	Chi-squared

Statistical analysis title	Decrease in NYHA class
Comparison groups	Group A, iron isomaltoside 1000 v Group B, placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8475
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time a subject had signed the ICF and until he/she has completed the study, all AEs/SAEs were collected in the CRF. SAEs occurring after study completion were reported, if considered related to the trial treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Group A, iron isomaltoside 1000

Reporting group description:

Subjects in the iron isomaltoside 1000 group received iron isomaltoside 1000 as a single dose infusion of 1000 mg over 15 min with a maximum single dose of 20 mg/kg.

Reporting group title	Group B, placebo

Reporting group description:

Subjects in the placebo group received saline (Natriumklorid 9 mg/mL, Fresenius Kabi, Copenhagen, Denmark) as a single dose infusion of 100 mL over 15 min.

Serious adverse events	Group A, iron isomaltoside 1000	Group B, placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 30 (26.67%)	9 / 30 (30.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft occlusion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft thrombosis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (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			
Pneumonia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (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 1000	Group B, placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 30 (63.33%)	24 / 30 (80.00%)	
Investigations			
Blood creatine phosphokinase MB increased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Haemoglobin decreased			
subjects affected / exposed	4 / 30 (13.33%)	4 / 30 (13.33%)	
occurrences (all)	4	4	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 30 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	11 / 30 (36.67%)	10 / 30 (33.33%)	
occurrences (all)	11	10	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Pleural effusion			
subjects affected / exposed	2 / 30 (6.67%)	6 / 30 (20.00%)	
occurrences (all)	2	6	
Respiratory failure			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Infection			
subjects affected / exposed	4 / 30 (13.33%)	1 / 30 (3.33%)	
occurrences (all)	4	1	
Oral candidiasis			
subjects affected / exposed	3 / 30 (10.00%)	4 / 30 (13.33%)	
occurrences (all)	3	4	
Pneumonia			
subjects affected / exposed	3 / 30 (10.00%)	2 / 30 (6.67%)	
occurrences (all)	4	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 August 2011	• In the inclusion criterion no. 3, the Hb level for women was changed from "< 12.0 g/dL (7.3 mmol/L)" to "< 11.5 g/dL (7.1 mmol/L)" • Impaired renal function was added as exclusion criteria no. 15 • Stratification by diagnostic group and baseline Hb level was added to the randomisation procedure • Blood transfusion was added to the list of protocol deviations, however patients requiring blood transfusion would not be withdrawn from the study • Dosing was to be done at the time of surgery when the patient was under anaesthesia to ensure blinding • Mean corpuscular Hb, globulin, and albumin:globulin ratio were deleted from the list of laboratory assessments • "Natriumklorid" was specifically mentioned as the placebo used for reference therapy • List of concomitant medications administered as part of the standard procedure in patients undergoing elective or sub-acute CABG, valve replacement, or a combination were added as Appendix 2 • List of AEs known to occur during surgery or postoperatively after the cardiac surgery were added as Appendix 3
20 December 2011	• Secondary objectives were added in accordance to the secondary endpoints • Secondary endpoint no. 6 was modified from number of patients in each randomisa-tion group who experience any "Suspected Unexpected Serious Adverse Event (SU-SAR)" to "study drug related adverse events (AEs/SAEs/SUSARs)" • Description of body measurements and six minute walking distance test was added to the study assessments • Analysis of laboratory parameters was to be conducted at the "local laboratory" in-stead of the "central laboratory" • Unblinding was to performed by the study nurse at the Department of Cardiothoracic Surgery • The safety reporting and study management sections were modified to reflect that Pharmacosmos A/S was the sponsor of the study and MNI was the sponsor designee for pharmacovigilance • Safety review by safety review committee was added • Time points for efficacy assessments were mentioned as: at baseline, 4 weeks, and 3 months postoperatively • Statistical methods for analyses of the number of patients who need blood transfusion, number of postoperative days to discharge, and change in six-minute walking distance from baseline to 4 weeks postoperatively were added • Role and responsibility of the investigator during an audit was added

15 November 2012	• The study population was changed from anaemic to non-anaemic • Dose of iron isomaltoside 1000 was changed from "20 mg/kg" to "1000 mg" • Addition and deletion of secondary endpoints. Two secondary endpoints "proportion of patients that are anaemic (women < 12 g/dL and men < 13 g/dL) at day 5 and week 4" and "proportion of patients able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at day 5 and week 4" were added, and the endpoint "change in Hb concentrations from baseline (preoperatively – the day before surgery or same day) to 3 months postoperatively" was deleted • The secondary endpoint "change of reticulocytes from baseline" was changed from 4 weeks and 3 months to day 5 and week 4 • Duration of the study for each individual patient was changed from "3 months" to "4 weeks" • Inclusion criterion 3 was revised where Hb level for women was changed from "< 11.5 g/dL (7.1 mmol/L)" to "≥ 12.0 g/dL (7.45 mmol/L)" and from "< 13.0 g/dL (8.1 mmol/L)" to "≥ 13.0 g/dL (8.1 mmol/L)" for men • Additional exclusion criterion "patients receiving blood transfusion < 30 days before screening and/or during the elective or sub-acute CABG, valve replacement, or a com-bination thereof" was added • Minor revisions in statistical analyses section were done, including revision of the def-inition of PP population and the number of randomised patients were changed from "80" to "60"
21 March 2013	• Six minute walking distance was replaced by NYHA classification • Instead of analysis of co-variance model, chi-square test was used to compare the average change in NYHA classification

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported