



## 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          | v1            |
| This version publication date  | 16 March 2016 |
| First version publication date | 16 July 2015  |

### 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  $\geq 18$  years of age undergoing elective or sub-acute CABG, valve replacement, or a combination thereof, with a Hb  $\geq 12.0$  g/dL (7.45 mmol/L) for women and a Hb  $\geq 13.0$  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                             |
| <b>Arm title</b>             | 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.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | 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                 |

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**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

| <b>Number of subjects in period 1</b> | 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<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                     |                         |                                |
| Age continuous  |                     |                         |                                |
| Age is calculated by subtracting the screening visit date with the birth date.  |                     |                         |                                |
| Units: years  |                     |                         |                                |
| arithmetic mean   | 65.2                | 66                      | 66.5                           |
| standard deviation  | ± 9.4               | ± 8.7                   | ± 8                            |
| Gender categorical  |                     |                         |                                |
| Units: Subjects   |                     |                         |                                |
| Female  | 8                   | 6                       | 6                              |
| Male  | 52                  | 45                      | 37                             |

## End points

### End points reporting groups

|  |                                 |
|--|---------------------------------|
| Reporting group title  | Group A, iron isomaltoside 1000 |
| Reporting group description:<br>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:<br>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:<br>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:<br>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:<br>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:<br>Change in Hb concentrations from baseline (preoperatively – the day before surgery or the same day) to 4 weeks postoperatively.<br><br>The analysis is performed on the FAS. |   |
| End point type   | Primary   |
| End point timeframe:<br>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

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Superiority tested by ANCOVA                       |
| Statistical analysis description:<br>An ANCOVA model was used to compare the average change in Hb concentration from baseline to week 4.<br>The number of subjects may differ from the analysis population if data is missing.<br>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 <sup>[1]</sup>                         |
| 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:<br>Change in Hb concentrations from baseline (preoperatively – the day before surgery or the same day) to 4 weeks postoperatively.<br><br>The analysis is performed on the PP analysis set. |  |
| End point type   | Primary  |
| End point timeframe:<br>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 <sup>[2]</sup>                         |
| 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

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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  |

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

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|                 |   |
|-----------------|---|
| 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.

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| 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**

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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                                       |

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

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

---

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 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. |  |
| 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 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.

|   |  |
|---|--|
| 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 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.

|   |  |
|---|--|
| 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 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. |  |
| 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 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.

|   |  |
|---|--|
| 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 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.

|   |  |
|---|--|
| 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 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. |  |
| 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 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. |  |
| 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 ( $\pm$ 3.38)              | 7.96 ( $\pm$ 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

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 %

| <b>Non-serious adverse events</b>                     | Group A, iron isomaltoside 1000 | Group B, placebo |  |
|---|---------------------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                                 |                  |  |
| subjects affected / exposed                           | 24 / 30 (80.00%)                | 27 / 30 (90.00%) |  |
| 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                |  |
| 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               |  |
| 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   | <ul style="list-style-type: none"><li>• In the inclusion criterion no. 3, the Hb level for women was changed from "&lt; 12.0 g/dL (7.3 mmol/L)" to "&lt; 11.5 g/dL (7.1 mmol/L)"</li><li>• Impaired renal function was added as exclusion criteria no. 15</li><li>• Stratification by diagnostic group and baseline Hb level was added to the randomisation procedure</li><li>• Blood transfusion was added to the list of protocol deviations, however patients requiring blood transfusion would not be withdrawn from the study</li><li>• Dosing was to be done at the time of surgery when the patient was under anaesthesia to ensure blinding</li><li>• Mean corpuscular Hb, globulin, and albumin:globulin ratio were deleted from the list of laboratory assessments</li><li>• "Natriumchlorid" was specifically mentioned as the placebo used for reference therapy</li><li>• 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</li><li>• List of AEs known to occur during surgery or postoperatively after the cardiac surgery were added as Appendix 3</li></ul>   |
| 20 December 2011 | <ul style="list-style-type: none"><li>• Secondary objectives were added in accordance to the secondary endpoints</li><li>• Secondary endpoint no. 6 was modified from number of patients in each randomisation group who experience any "Suspected Unexpected Serious Adverse Event (SU-SAR)" to "study drug related adverse events (AEs/SAEs/SUSARs)"</li><li>• Description of body measurements and six minute walking distance test was added to the study assessments</li><li>• Analysis of laboratory parameters was to be conducted at the "local laboratory" instead of the "central laboratory"</li><li>• Unblinding was to be performed by the study nurse at the Department of Cardiothoracic Surgery</li><li>• 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</li><li>• Safety review by safety review committee was added</li><li>• Time points for efficacy assessments were mentioned as: at baseline, 4 weeks, and 3 months postoperatively</li><li>• 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</li><li>• Role and responsibility of the investigator during an audit was added</li></ul> |

|                  |  |
|------------------|--|
| 15 November 2012 | <ul style="list-style-type: none"> <li>• The study population was changed from anaemic to non-anaemic</li> <li>• Dose of iron isomaltoside 1000 was changed from "20 mg/kg" to "1000 mg"</li> <li>• Addition and deletion of secondary endpoints. Two secondary endpoints "proportion of patients that are anaemic (women &lt; 12 g/dL and men &lt; 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</li> <li>• The secondary endpoint "change of reticulocytes from baseline" was changed from 4 weeks and 3 months to day 5 and week 4</li> <li>• Duration of the study for each individual patient was changed from "3 months" to "4 weeks"</li> <li>• Inclusion criterion 3 was revised where Hb level for women was changed from "&lt; 11.5 g/dL (7.1 mmol/L)" to "≥ 12.0 g/dL (7.45 mmol/L)" and from "&lt; 13.0 g/dL (8.1 mmol/L)" to "≥ 13.0 g/dL (8.1 mmol/L)" for men</li> <li>• Additional exclusion criterion "patients receiving blood transfusion &lt; 30 days before screening and/or during the elective or sub-acute CABG, valve replacement, or a combination thereof" was added</li> <li>• Minor revisions in statistical analyses section were done, including revision of the definition of PP population and the number of randomised patients were changed from "80" to "60"</li> </ul> |
| 21 March 2013    | <ul style="list-style-type: none"> <li>• Six minute walking distance was replaced by NYHA classification</li> <li>• Instead of analysis of co-variance model, chi-square test was used to compare the average change in NYHA classification</li> </ul>   |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported