



## Clinical trial results:

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

### Summary

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

### Results information

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

### Trial information

#### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | P-Monofer-IBD-03 |
|-----------------------|------------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03466983 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 04 January 2021 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 25 May 2020     |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 25 May 2020     |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy:

None.

Evidence for comparator:

Abbreviations used in this study entry

AE=Adverse event

D=Day

eGFR=Estimated Glomerular Filtration Rate

GCP=Good Clinical Practice

IBD=Inflammatory bowel disease

ICF=Informed consent form

IDA=Iron deficiency anaemia

ITT=Intention to treat

IV=Intravenous

SAE=Serious adverse event

TSAT=Transferrin saturation

W=Week

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 23 May 2018 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | No          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 18 |
| Country: Number of subjects enrolled | Austria: 42        |
| Country: Number of subjects enrolled | Denmark: 22        |
| Country: Number of subjects enrolled | Germany: 13        |
| Country: Number of subjects enrolled | Sweden: 2          |
| Worldwide total number of subjects   | 97                 |
| EEA total number of subjects         | 97                 |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 88 |
| From 65 to 84 years                       | 9  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

Men and women aged  $\geq 18$  years with IBD and with Hb  $< 13$  g/dL, body weight  $\geq 50$  kg, s-ferritin  $\leq 100$  ng/mL, eGFR  $\geq 65$  mL/min/1.73 m<sup>2</sup>, s-phosphate  $> 2.5$  mg/dL, and where oral iron preparations were ineffective or could not be used or where there was a clinical need to deliver iron rapidly, were allowed to participate after signing the ICF.

### Period 1

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

Blinding implementation details:

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

### Arms

|                              |                            |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes                        |
| <b>Arm title</b>             | Group A, iron isomaltoside |

Arm description:

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

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

Dosage and administration details:

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

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

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Group B, ferric carboxymaltose |
|------------------|--------------------------------|

Arm description:

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

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

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

Dosage and administration details:

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

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

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

## Baseline characteristics

### Reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Group A, iron isomaltoside |
|-----------------------|----------------------------|

Reporting group description:

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

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Group B, ferric carboxymaltose |
|-----------------------|--------------------------------|

Reporting group description:

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

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

## End points

### End points reporting groups

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

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

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

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

Notes:

[1] - Safety analysis set

[2] - Safety analysis set

### Statistical analyses

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

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

## Secondary: 2\_Haemoglobin - Change from baseline

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | 2_Haemoglobin - Change from baseline |
|-----------------|--------------------------------------|

End point description:

Change in haemoglobin from baseline to prespecified days up to Week 10 . The number of subjects included in the evaluation at each timepoint:

Iron Isomaltoside

D1 N=48

W1 N=45

W2 N=46

W5 N=42

W6 N=43

W7 N=42

W10 N=43

Ferric Carboxymaltose

D1 N=48

W1 N=44

W2 N=47

W5 N=44

W6 N=41

W7 N=43

W10 N=41

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

|         |                    |                    |  |  |
|---------|--------------------|--------------------|--|--|
| Week 7  | 2.36 ( $\pm$ 1.27) | 2.38 ( $\pm$ 1.23) |  |  |
| Week 10 | 2.51 ( $\pm$ 1.41) | 2.44 ( $\pm$ 1.49) |  |  |

Notes:

[3] - ITT

[4] - ITT

## Statistical analyses

|                                   |       |
|-----------------------------------|-------|
| <b>Statistical analysis title</b> | Day 1 |
|-----------------------------------|-------|

Statistical analysis description:

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

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

|                                   |        |
|-----------------------------------|--------|
| <b>Statistical analysis title</b> | Week 1 |
|-----------------------------------|--------|

Statistical analysis description:

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

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

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Week 2  |
| Statistical analysis description:  |   |
| The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix was used to model the within-subject errors. |   |
| Comparison groups  | Group A, iron isomaltoside v Group B, ferric carboxymaltose |
| Number of subjects included in analysis  | 97  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | = 0.9393  |
| Method   | mixed model for repeated measures                           |
| Parameter estimate   | Mean difference (final values)                              |
| Point estimate   | 0.011   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -0.283  |
| upper limit  | 0.305   |

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Week 5  |
| Statistical analysis description:  |   |
| The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix was used to model the within-subject errors. |   |
| Comparison groups  | Group A, iron isomaltoside v Group B, ferric carboxymaltose |
| Number of subjects included in analysis  | 97  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | = 0.7778  |
| Method   | mixed model for repeated measures                           |
| Parameter estimate   | Mean difference (final values)                              |
| Point estimate   | -0.053  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -0.427  |
| upper limit  | 0.321   |

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Week 6  |
| Statistical analysis description:  |   |
| The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix was used to model the within-subject errors. |   |
| Comparison groups  | Group A, iron isomaltoside v Group B, ferric carboxymaltose |

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

|                                   |        |
|-----------------------------------|--------|
| <b>Statistical analysis title</b> | Week 7 |
|-----------------------------------|--------|

Statistical analysis description:

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

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

|                                   |         |
|-----------------------------------|---------|
| <b>Statistical analysis title</b> | Week 10 |
|-----------------------------------|---------|

Statistical analysis description:

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

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

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

### Secondary: 3\_s-ferritin - Change from baseline

|                 |                                     |
|-----------------|-------------------------------------|
| End point title | 3_s-ferritin - Change from baseline |
|-----------------|-------------------------------------|

End point description:

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

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

Iron Isomaltoside

D1 N=48

W1 N=46

W2 N=46

W5 N=43

W6 N=42

W7 N=42

W10 N=45

Ferric Carboxymaltose

D1 N=47

W1 N=46

W2 N=47

W5 N=44

W6 N=42

W7 N=42

W10 N=42

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

|         |                        |                        |  |  |
|---------|------------------------|------------------------|--|--|
| Week 10 | 127.13 ( $\pm$ 130.70) | 116.16 ( $\pm$ 101.75) |  |  |
|---------|------------------------|------------------------|--|--|

Notes:

[5] - ITT analysis set

[6] - ITT analysis set

## Statistical analyses

|                                   |       |
|-----------------------------------|-------|
| <b>Statistical analysis title</b> | Day 1 |
|-----------------------------------|-------|

Statistical analysis description:

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

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

|                                   |        |
|-----------------------------------|--------|
| <b>Statistical analysis title</b> | Week 1 |
|-----------------------------------|--------|

Statistical analysis description:

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

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

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Week 2  |
| Statistical analysis description:  |   |
| The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors. |   |
| Comparison groups  | Group A, iron isomaltoside v Group B, ferric carboxymaltose |
| Number of subjects included in analysis  | 97  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | = 0.6104  |
| Method   | mixed model for repeated measures                           |
| Parameter estimate   | Mean difference (final values)                              |
| Point estimate   | -11.28  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -55.11  |
| upper limit  | 32.54   |

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Week 5  |
| Statistical analysis description:  |   |
| The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors. |   |
| Comparison groups  | Group A, iron isomaltoside v Group B, ferric carboxymaltose |
| Number of subjects included in analysis  | 97  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | = 0.6214  |
| Method   | mixed model for repeated measures                           |
| Parameter estimate   | Mean difference (final values)                              |
| Point estimate   | 6.38  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -19.2   |
| upper limit  | 31.96   |

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Week 6  |
| Statistical analysis description:  |   |
| The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors. |   |
| Comparison groups  | Group A, iron isomaltoside v Group B, ferric carboxymaltose |

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

|                                   |        |
|-----------------------------------|--------|
| <b>Statistical analysis title</b> | Week 7 |
|-----------------------------------|--------|

Statistical analysis description:

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

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

|                                   |         |
|-----------------------------------|---------|
| <b>Statistical analysis title</b> | Week 10 |
|-----------------------------------|---------|

Statistical analysis description:

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

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

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

### Secondary: 4\_TSAT - Change from baseline

|                 |                               |
|-----------------|-------------------------------|
| End point title | 4_TSAT - Change from baseline |
|-----------------|-------------------------------|

End point description:

Change in TSAT from baseline to prespecified days up to Week 10. The number of subjects included in the evaluation at each timepoint:

Iron Isomaltoside

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

Ferric Carboxymaltose

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

[7] - ITT Analysis set

[8] - ITT Analysis set

## Statistical analyses

| Statistical analysis title   | Day 1   |
|--|---|
| Statistical analysis description:  |   |
| The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors. |   |
| Comparison groups  | Group A, iron isomaltoside v Group B, ferric carboxymaltose |
| Number of subjects included in analysis  | 97  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | < 0.0001  |
| Method   | mixed model for repeated measures                           |
| Parameter estimate   | Mean difference (final values)                              |
| Point estimate   | 42.06   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 26.03   |
| upper limit  | 58.08   |
| Variability estimate   | Standard error of the mean                                  |

| Statistical analysis title   | Week 1  |
|--|---|
| Statistical analysis description:  |   |
| The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors. |   |
| Comparison groups  | Group A, iron isomaltoside v Group B, ferric carboxymaltose |
| Number of subjects included in analysis  | 97  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | = 0.1822  |
| Method   | mixed model for repeated measures                           |
| Parameter estimate   | Mean difference (final values)                              |
| Point estimate   | 4.25  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -2.04   |
| upper limit  | 10.54   |
| Variability estimate   | Standard error of the mean                                  |

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Week 2  |
| Statistical analysis description:  |   |
| The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors. |   |
| Comparison groups  | Group B, ferric carboxymaltose v Group A, iron isomaltoside |
| Number of subjects included in analysis  | 97  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | = 0.809   |
| Method   | mixed model for repeated measures                           |
| Parameter estimate   | Mean difference (final values)                              |
| Point estimate   | 0.49  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -3.55   |
| upper limit  | 4.54  |
| Variability estimate   | Standard error of the mean                                  |

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Week 5  |
| Statistical analysis description:  |   |
| The model included the fixed, categorical effects of treatment (iron isomaltoside and ferric carboxymaltose), stratum, day, treatment-by-day interaction, as well as the continuous, fixed covariates of the parameters baseline value and baseline value-by-day interaction. An unstructured covariance matrix will be used to model the within-subject errors. |   |
| Comparison groups  | Group A, iron isomaltoside v Group B, ferric carboxymaltose |
| Number of subjects included in analysis  | 97  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | = 0.2011  |
| Method   | mixed model for repeated measures                           |
| Parameter estimate   | Mean difference (final values)                              |
| Point estimate   | 2.98  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -1.62   |
| upper limit  | 7.58  |
| Variability estimate   | Standard error of the mean                                  |

|                                   |        |
|-----------------------------------|--------|
| <b>Statistical analysis title</b> | Week 6 |
|-----------------------------------|--------|

**Statistical analysis description:**

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

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

**Statistical analysis title** | Week 7**Statistical analysis description:**

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

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

**Statistical analysis title** | Week 10**Statistical analysis description:**

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

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

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

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the time of signing the ICF and to trial completion or discontinuation.

Adverse event reporting additional description:

The investigator described the nature of the AE/SAEs, using the standard medical terminology. If known, a specific diagnosis was stated.

Safety Analysis Set was used for evaluation of the AE/SAEs;

Safety Analysis Set = All subjects who received at least one dose of the trial drug.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20.1   |

### Reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Group A, iron isomaltoside |
|-----------------------|----------------------------|

Reporting group description:

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

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Group B, ferric carboxymaltose |
|-----------------------|--------------------------------|

Reporting group description:

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

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

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

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 08 September 2017 | <ul style="list-style-type: none"><li>• Change of exclusion criterion 20 from 'Pregnant or nursing women. In order to avoid pregnancy, women of childbearing potential have to use adequate contraception (e.g. intrauterine devices, hormonal contraceptives, or double barrier method) during the whole trial period and 7 days after the last dosing' to 'Pregnant or nursing women. In order to avoid pregnancy, women of childbearing potential have to use highly efficient contraception (e.g. intrauterine devices, hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release)) during the whole trial period and 7 days after the last dosing. A sterile sole partner or sexual abstinence is also considered acceptable provided it reflects the usual and preferred lifestyle of the participant' due to a requirement from the Competent Authority in Denmark.</li></ul>   |
| 06 November 2017  | <ul style="list-style-type: none"><li>• Deletion of the exclusion criterion 'Active malignant disease, disease-free for less than 5 years' since exclusion of oncology patients was a mistake.</li><li>• Deletion of the stratification based on type of underlying disease, as this was originally included in the protocol by mistake.</li><li>• Correction of the volume of ferric carboxymaltose single-use vials from 15 mL to 20 mL in order to align with the available vial size.</li><li>• Clarification that dilution of iron isomaltoside and ferric carboxymaltose was to a total volume of 100 mL instead of in 100 mL 0.9 % sodium chloride.</li><li>• Clarification that the Ferinject® SmPC was the only reference document for choice of dose, investigational product administration, and SUSAR definition for ferric carboxymaltose.</li><li>• Specification of TCT members (change from 'QC/Regulatory' to 'Quality Assurance', 'Quality Control', and 'Regulatory') in order to reflect the current TCT members.</li></ul> |

|                  |  |
|------------------|--|
| 06 November 2017 | <ul style="list-style-type: none"> <li>• Change of trial design from open-label to double-blind in order to increase the scientific value of the trial.</li> <li>• Change of inclusion criteria 3 and 4 from 'Hb &lt; 10 g/dL' and 'Body weight &gt; 70 kg' to 'Hb &lt; 13 g/dL' and 'Body weight ≥ 50 kg' in order to be able to include subjects with a need of a cumulative dose of 1500 mg iron and obtain information on the safety and efficacy of iron isomaltoside in this group of subjects.</li> <li>• Addition of exclusion criterion 2 'Hb ≥ 10 g/dL and body weight &lt; 70 kg' in order to ensure an iron need of minimum 1500 mg.</li> <li>• Change of dosing regimen from 1000 mg at baseline and at day 35 to 1000 mg at baseline and 500 or 1000 mg at day 35, i.e. the cumulative dose was changed from 2000 mg to 1500 or 2000 mg, in order to be able to include subjects with a need of a cumulative dose of 1500 mg iron.</li> <li>• Specification that the cumulative dose of 1500 or 2000 mg was dependent on the subject's screening Hb and body weight.</li> <li>• Change of infusion time for ferric carboxymaltose from at least 15 minutes to approximately 20 minutes.</li> <li>• Deletion of the exclusion criterion 'History of a psychological illness or seizures' since no contraindications or warnings related to psychological illness or seizures are included in the SmPC.</li> <li>• Deletion of the visit at week 13, thereby having week 10 as the last visit, in order to ease the burden on the subjects.</li> <li>• Addition of ESAs, radiotherapy, and chemotherapy to the list of prohibited medication and non-drug therapies in order to ensure alignment with the exclusion criteria.</li> <li>• Deletion of the measurement of pyridinoline in urine, since this was an exploratory endpoint with a limited value, which showed to be quite challenging to both site and subjects due to very specific requirements of the urine sample.</li> <li>• Clarification that alkaline phosphatase was measured in serum rather than in plasma.</li> </ul> |
| 12 January 2018  | <ul style="list-style-type: none"> <li>• The following was added as a note to exclusion criterion 2 for clarification: 'To ensure an iron need of minimum 1500 mg; subjects with a Hb ≥ 10 g/dL must have a body weight ≥ 70 kg. Subjects with a body weight of ≥ 50 kg to &lt; 70 kg are eligible only if Hb is below 10 mg/dL.'</li> <li>• In addition to the urine pregnancy test at baseline in all women of childbearing potential, a serum pregnancy test was added at screening and baseline for all women of childbearing potential enrolled in UK due to a requirement from the Competent Authority in UK.</li> </ul>   |
| 22 January 2018  | <ul style="list-style-type: none"> <li>• Deletion of the exclusion criterion 'Vitamin D deficiency' and deletion of vitamin D from the eligibility laboratory assessments, since it is not standard clinical practice to measure vitamin D prior to IV iron treatment.</li> <li>• Addition of details related to the blinding and randomisation procedures.</li> </ul>   |

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| 15 July 2019 | <ul style="list-style-type: none"> <li>• Clarification that exploratory safety endpoints were to be analysed using the safety analysis set, while exploratory efficacy endpoints were to be analysed using the ITT analysis set.</li> <li>• Clarification that for the statistical analyses of change from baseline in Hb, s-ferritin, and TSAT, subjects without post-baseline assessments were to have change from baseline = 0 imputed at the first post-baseline visit.</li> <li>• Change of exclusion criterion 7 from 'Treatment with erythropoietin or ESAs, red blood cell transfusion, radiotherapy, and/or chemotherapy within the last 30 days prior to screening' to 'Treatment with erythropoietin or ESAs, red blood cell transfusion, radiotherapy, and/or chemotherapy (except immune modulating therapy for standard IBD treatment) within the last 30 days prior to screening' for clarification.</li> <li>• The following clarifications were made to the list of prohibited medication: 'Any iron supplementation other than investigational drug (nutritional supplementation including iron is allowed unless it is assumed as treatment of the subject's anaemia)' changed to 'Any iron supplementation other than investigational drug (multivitamins including iron is allowed unless it is assumed as treatment of the subject's anaemia)' and 'Chemotherapy' changed to 'Chemotherapy (except immune modulating therapy for standard IBD treatment)'.</li> <li>• Inclusion of baseline body weight and baseline Hb as additional covariates in the sensitivity analysis of the primary endpoint.</li> <li>• Change of safety reference document for iron isomaltoside from the Monofer® Investigator's Brochure to the Monofer® SmPC since treatment with iron isomaltoside in this trial was within the label and the same SmPC is approved in all the participating countries.</li> </ul>  |
| 15 July 2019 | <ul style="list-style-type: none"> <li>• Omission of iFGF23 from the eligibility laboratory assessments at screening as iFGF23 was not part of any inclusion or exclusion criteria or stratification.</li> <li>• Deletion of the secondary safety objective 'To compare the effects of iron isomaltoside and ferric carboxymaltose treatment in subjects with IDA due to IBD on proportion of subjects with hypophosphatemia at the last visit' since this objective is already covered in the primary objective.</li> <li>• In the primary endpoint, the definition of hypophosphatemia was further detailed and the unit used for the time period was changed from days to weeks.</li> <li>• In the secondary safety endpoints, 's phosphate &lt; 1.0 mg/dL' was changed to 's phosphate ≤ 1.0 mg/dL' in order to align with previous trials with iron isomaltoside.</li> <li>• Change of the endpoint 'Incidence of s-phosphate &lt; 1.0 mg/dL at any time from baseline to day 35' to 'Incidence of s-phosphate ≤ 1.0 mg/dL at any time from baseline to week 5 and at any time from baseline to week 10' in order to align with previous trials with iron isomaltoside.</li> <li>• Addition of the secondary safety endpoints, 'Incidence of hypophosphatemia at day 1 and weeks 1, 2, 5, 6, 7, and 10' and 'Incidence of s phosphate ≤ 1.0 mg/dL at day 1 and weeks 1, 2, 5, 6, 7, and 10', including description of statistical analyses of these endpoints, in order to align with previous trials with iron isomaltoside.</li> <li>• Clarification that the secondary safety endpoint on fractional phosphate urinary excretion was derived as change from baseline to day 1 and weeks 1, 2, 5, 6, 7, and 10.</li> <li>• Change and expansion of the statistical analysis of AEs from 'Number of subjects who experience an ADR including SUSARs will be compared between treatment groups' to 'The incidence of TEAEs, SAEs, ADRs including SUSARs as well as SARs will be compared between treatment groups' in order to align with previous trials with iron isomaltoside.</li> </ul> |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported