



## Clinical trial results:

**Multicentre, prospective, randomised, 2-arm study to assess the impact of ferric carboxymaltose on exercise capacity in chronic heart failure patients with iron deficiency.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-000603-40 |
| Trial protocol           | BE NL DE IT ES |
| Global end of trial date | 18 May 2016    |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 01 June 2017 |
| First version publication date | 01 June 2017 |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | FER-CARS-04 |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01394562 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Vifor (International) Inc.   |
| Sponsor organisation address | Rechenstrasse 37, St. Gallen, Switzerland, CH-9001                                     |
| Public contact               | Medical Information, Vifor (International) Inc., 41 588518222, medinfo@viforpharma.com |
| Scientific contact           | Medical Information, Vifor (International) Inc., 41 588518222, medinfo@viforpharma.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 27 March 2017 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 18 May 2016   |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

Primary objective of the trial is to evaluate the effect of intravenous (IV) ferric carboxymaltose (FCM) compared to standard of care (SoC) on exercise capacity as assessed by weight-adjusted peak oxygen uptake (VO<sub>2</sub>).

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki including amendments in force up to and including the time the study was conducted. The study was conducted in compliance with the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), Committee for Proprietary Medicinal Products Guideline (CPMP/ICH/135/95), and compliant with the EU Clinical Trial Directive (Directive 2001/20/EC) and/or the Code of Federal Regulations (CFR) for informed consent and protection of patient rights (21 CFR, Parts 50 and 56). Before each subject was admitted to the study, a signed and dated informed consent was obtained from the subject (or his/her legally authorised representative) according to the regulatory and legal requirements of the participating country. This consent form was retained by the Investigator as part of the study records. A copy of the document was provided to the subject. No investigations specifically required for the study were conducted until valid consent was obtained.

The Investigator explained the aims, methods, reasonably anticipated benefits and potential hazards of the study and any potential discomforts. Subjects were informed that their participation in the study was entirely voluntary and would have no effect on clinical care otherwise available and that they could withdraw consent to participate at any time without penalty or loss of further medical treatment. Subjects were told that competent authorities and authorized persons could examine their records but that personal information would be treated as strictly confidential and would not be publicly available.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 08 September 2011 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Netherlands: 22        |
| Country: Number of subjects enrolled | Poland: 36             |
| Country: Number of subjects enrolled | Spain: 10              |
| Country: Number of subjects enrolled | Belgium: 8             |
| Country: Number of subjects enrolled | France: 10             |
| Country: Number of subjects enrolled | Germany: 24            |
| Country: Number of subjects enrolled | Italy: 18              |
| Country: Number of subjects enrolled | Russian Federation: 42 |
| Country: Number of subjects enrolled | Australia: 4           |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 174 |
| EEA total number of subjects       | 128 |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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)                      | 90 |
| From 65 to 84 years                       | 82 |
| 85 years and over                         | 2  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted in 28 centres in 9 countries. 41 centres participated in the study; 35 centres screened 525 subjects, and 28 centres randomized 174 subjects into two arms of the study: 88 to the FCM group and 86 to the SoC group.

### Pre-assignment

Screening details:

After an initial screening period (up to 12 weeks) eligible subjects were randomised (1:1) to FCM or SoC for a period of up to 24 weeks. A total of 174 subjects were randomised in 28 centres across 9 countries. Randomised 1:1 received either IV FCM injection/infusion or SoC. Stratification by Hb (Haemoglobin) level (<12 g/dl, ≥12 g/dl).

### Period 1

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

Blinding implementation details:

This study was conducted as an open-label study. To minimise bias, the readings for the primary endpoint (peak VO<sub>2</sub>) were completed by an independent consultant unaware of subject treatment. All peak VO<sub>2</sub> assessments were recalculated by the centralised CORELAB which was blinded to all subject and visit identifiers. Echocardiography (ECHO) assessments were conducted in a blinded manner by the ECHOLAB, and New York Heart Association (NYHA) assessments were performed by a blinded physician.

### Arms

|                              |                             |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes                         |
| <b>Arm title</b>             | Ferric carboxymaltose (FCM) |

Arm description:

FCM solution (Ferinject) for IV bolus injection/IV infusion, 50 mg/mL iron. Dosing of FCM on Day 1 and Week 6 was based on screening haemoglobin (Hb) and screening weight. Further maintenance dosing of 500 mg iron at Week 12 was administered if serum ferritin <100 ng/mL or ferritin between 100- <300 ng/mL with transferrin saturation (TSAT) <20%.

|  |  |
|--|--|
| Arm type                               | Experimental                           |
| Investigational medicinal product name | Ferric carboxymaltose                  |
| Investigational medicinal product code |  |
| Other name                             | FCM, Ferinject                         |
| Pharmaceutical forms                   | Solution for injection/infusion        |
| Routes of administration               | Intravenous use, Intravenous bolus use |

Dosage and administration details:

FCM solution containing 5% w/v iron; doses of 500 mg iron (10 mL) or 1,000 mg iron (20 mL). FCM was administered as either an undiluted bolus IV injection or by IV infusion by designated staff at each site. For bolus injection, FCM was to be administered over at least 1 minute. For IV infusion, FCM was diluted in sterile 0.9% sodium chloride (saline): i.e., 500 mg (10 mL) diluted into approximately 100 mL saline and administered over at least 6 minutes; or 1,000 mg (20 mL) diluted into approximately 250 mL saline and administered over at least 15 minutes. All administrations, including duration of injection/infusion and if the injection/infusion was interrupted/stopped, and any related information, were documented in the site source data and in the Case Report Form (CRF).

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Standard of Care (SoC) |
|------------------|------------------------|

Arm description:

Subjects' Iron deficiency (ID) was to be managed per the SoC at the treating institution. Subjects randomised to SoC were permitted to receive oral iron at the Investigator's discretion; however, IV iron was not permitted.

|          |                 |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

| Number of subjects in period 1        | Ferric carboxymaltose (FCM) | Standard of Care (SoC) |
|---------------------------------------|-----------------------------|------------------------|
|                                       |                             |                        |
| Started                               | 88                          | 86                     |
| Treated                               | 88                          | 85                     |
| Completed                             | 81                          | 81                     |
| Not completed                         | 7                           | 5                      |
| Adverse event, serious fatal          | -                           | 4                      |
| Consent withdrawn by subject          | 2                           | -                      |
| Company decision (protocol violation) | 1                           | 1                      |
| not specified reason                  | 2                           | -                      |
| Adverse event, non-fatal              | 1                           | -                      |
| Lost to follow-up                     | 1                           | -                      |

## Baseline characteristics

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Ferric carboxymaltose (FCM) |
|-----------------------|-----------------------------|

Reporting group description:

FCM solution (Ferinject) for IV bolus injection/IV infusion, 50 mg/mL iron. Dosing of FCM on Day 1 and Week 6 was based on screening haemoglobin (Hb) and screening weight. Further maintenance dosing of 500 mg iron at Week 12 was administered if serum ferritin <100 ng/mL or ferritin between 100- <300 ng/mL with transferrin saturation (TSAT) <20%.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Standard of Care (SoC) |
|-----------------------|------------------------|

Reporting group description:

Subjects' Iron deficiency (ID) was to be managed per the SoC at the treating institution. Subjects randomised to SoC were permitted to receive oral iron at the Investigator's discretion; however, IV iron was not permitted.

| Reporting group values                | Ferric carboxymaltose (FCM) | Standard of Care (SoC) | Total |
|---------------------------------------|-----------------------------|------------------------|-------|
| Number of subjects                    | 88                          | 86                     | 174   |
| Age categorical<br>Units: Subjects    |                             |                        |       |
| Adults (18-64 years)                  | 47                          | 43                     | 90    |
| From 65-84 years                      | 40                          | 42                     | 82    |
| 85 years and over                     | 1                           | 1                      | 2     |
| Age continuous<br>Units: years        |                             |                        |       |
| arithmetic mean                       | 62.7                        | 64.4                   |       |
| standard deviation                    | ± 11.45                     | ± 11.42                | -     |
| Gender categorical<br>Units: Subjects |                             |                        |       |
| Female                                | 61                          | 69                     | 130   |
| Male                                  | 27                          | 17                     | 44    |

## End points

### End points reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Ferric carboxymaltose (FCM) |
|-----------------------|-----------------------------|

Reporting group description:

FCM solution (Ferinject) for IV bolus injection/IV infusion, 50 mg/mL iron. Dosing of FCM on Day 1 and Week 6 was based on screening haemoglobin (Hb) and screening weight. Further maintenance dosing of 500 mg iron at Week 12 was administered if serum ferritin <100 ng/mL or ferritin between 100- <300 ng/mL with transferrin saturation (TSAT) <20%.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Standard of Care (SoC) |
|-----------------------|------------------------|

Reporting group description:

Subjects' Iron deficiency (ID) was to be managed per the SoC at the treating institution. Subjects randomised to SoC were permitted to receive oral iron at the Investigator's discretion; however, IV iron was not permitted.

|                            |                               |
|----------------------------|-------------------------------|
| Subject analysis set title | Full analysis set (FAS) - FCM |
|----------------------------|-------------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Full analysis set (FAS) consisted of all subjects randomised to FCM group, received at least 1 dose of randomised study treatment and attended at least 1 post-Baseline (BL) visit with valid efficacy data measurements.

Note: One subject was randomised to SoC but received FCM. This subject is counted in the SoC group for the FAS.

One subject was randomized to FCM, but did not receive treatment with the study drug and therefore, was excluded from the Full Analysis Set (FAS).

|                            |                               |
|----------------------------|-------------------------------|
| Subject analysis set title | Full analysis set (FAS) - SoC |
|----------------------------|-------------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Full analysis set (FAS) consisted of all subjects randomised to SoC group and attended at least 1 post-baseline visit with non-missing efficacy data measurement.

Note: The subject randomised to SoC who received FCM treatment is counted in the SoC group for the FAS.

|                            |                       |
|----------------------------|-----------------------|
| Subject analysis set title | Safety Set (SS) - FCM |
|----------------------------|-----------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Safety population consists of all randomised subjects who have received at least 1 dose of study medication.

|                            |                       |
|----------------------------|-----------------------|
| Subject analysis set title | Safety Set (SS) - SoC |
|----------------------------|-----------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Safety set consists of all randomised subjects for SoC group.

NOTE: One subject was randomised to SoC but received FCM and is therefore, not counted in the SoC arm for the SS, but in the FCM arm.

Another subject was randomized to FCM, but did not receive treatment with the study drug and therefore, was excluded from the Safety Set (SS).

### Primary: Change in peak VO<sub>2</sub> (mL/kg/min) from baseline to Week 24 (LOCF)

|                 |  |
|-----------------|--|
| End point title | Change in peak VO <sub>2</sub> (mL/kg/min) from baseline to Week 24 (LOCF) |
|-----------------|--|

End point description:

The primary efficacy endpoint of the study was the change in weight-adjusted peak VO<sub>2</sub> (mL/kg/min) from Baseline (BL) to Week 24 (LOCF).

Results are presented for the absolute values at BL and Week 24 (LOCF) and change value from BL to Week 24 (LOCF).

Imputation for death is equivalent to 0.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:  
From Baseline to Week 24 (LOCF)

| <b>End point values</b>                   | Full analysis set (FAS) - FCM | Full analysis set (FAS) - SoC |  |  |
|---|-------------------------------|-------------------------------|--|--|
| Subject group type                        | Subject analysis set          | Subject analysis set          |  |  |
| Number of subjects analysed               | 80                            | 81                            |  |  |
| Units: mL/kg/min                          |                               |                               |  |  |
| arithmetic mean (confidence interval 95%) |                               |                               |  |  |
| Baseline (absolute value) n=84, 85        | 13.55 (13.053 to 14.04)       | 13.36 (12.837 to 13.881)      |  |  |
| Week 24 LOCF (absolute value) n= 80, 81   | 13.5 (12.866 to 14.136)       | 12.34 (11.47 to 13.216)       |  |  |
| Week 24 LOCF (change from BL) n= 80, 81   | -0.08 (-0.578 to 0.413)       | -1.1 (-1.818 to -0.379)       |  |  |

## Statistical analyses

| <b>Statistical analysis title</b> | Changes in peak VO2 from BL to Week 24 (LOCF) |
|-----------------------------------|---|
|-----------------------------------|---|

Statistical analysis description:

For analysis of the primary endpoint (with Last Observation Carried Forward (LOCF) and imputation for deaths), a comparison between treatment groups was assessed using an ANCOVA model with adjustment for BL peak VO2, Hb level at screening (<12 g/dl, ≥12 g/dl), and pooled country. A second ANCOVA (sensitivity analysis) was conducted to examine the terms of interaction between pooled country and treatment group and between Hb level at screening and treatment group. Subjects in the analysis are 161.

|   |   |
|---|---|
| Comparison groups                       | Full analysis set (FAS) - FCM v Full analysis set (FAS) - SoC |
| Number of subjects included in analysis | 161   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0202 [1]  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Difference of Least Square Mean                               |
| Point estimate                          | 1.04  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.164   |
| upper limit                             | 1.909   |
| Variability estimate                    | Standard error of the mean                                    |
| Dispersion value                        | 0.442   |

Notes:

[1] - Significant difference at 5% significance level.

## Secondary: Peak VO2 Change from BL Over Time

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | Peak VO2 Change from BL Over Time |
|-----------------|-----------------------------------|

End point description:

The change in peak VO2 from BL over time (i.e., to Weeks 12 and 24) was analysed on observed cases (without any imputation) using an ANCOVA with repeated measures for the FAS with treatment, visit gender, age, BL score, pooled country and Hb level at screening (<12 g/dl or ≥12 g/dl) (FAS). Also interaction between visit and treatment.

End point type Secondary

End point timeframe:

Week 12, Week 24

| End point values                          | Full analysis set (FAS) - FCM | Full analysis set (FAS) - SoC |  |  |
|---|-------------------------------|-------------------------------|--|--|
| Subject group type                        | Subject analysis set          | Subject analysis set          |  |  |
| Number of subjects analysed               | 67                            | 68                            |  |  |
| Units: mL/kg/min                          |                               |                               |  |  |
| arithmetic mean (confidence interval 95%) |                               |                               |  |  |
| Week 12 n=67, 68                          | 13.82 (13.117 to 14.528)      | 13.24 (12.543 to 13.93)       |  |  |
| Week 24 n=66, 68                          | 13.69 (12.964 to 14.415)      | 13.23 (12.554 to 13.898)      |  |  |

## Statistical analyses

**Statistical analysis title** Peak VO2 Change from BL Over time -Week 12

Statistical analysis description:

Peak VO2 from BL over time at Week 12 was analysed on observed cases (without any imputation) using an ANCOVA with repeated measures with treatment, gender, age, BL score, pooled country, visit and Hb level at screening (<12 g/dl or ≥12 g/dl). Also interaction between visit and treatment. Subjects in this analysis are 135.

Comparison groups Full analysis set (FAS) - FCM v Full analysis set (FAS) - SoC

Number of subjects included in analysis 135

Analysis specification Pre-specified

Analysis type superiority

P-value = 0.24

Method Repeated measure ANCOVA

Parameter estimate Difference of Least-Square Means

Point estimate 0.45

Confidence interval

level 95 %

sides 2-sided

lower limit -0.306

upper limit 1.197

Variability estimate Standard error of the mean

Dispersion value 0.379

**Statistical analysis title** Peak VO2 Change from BL Over time -Week 24

Statistical analysis description:

Peak VO2 from BL over time at Week 24 was analysed on observed cases (without any imputation) using an ANCOVA with repeated measures, treatment, gender, age, BL score, pooled country, visit and Hb level at screening (<12 g/dl or ≥12 g/dl). Also interaction between visit and treatment. Subjects in this analysis are 134.

|   |   |
|---|---|
| Comparison groups                       | Full analysis set (FAS) - FCM v Full analysis set (FAS) - SoC |
| Number of subjects included in analysis | 135   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.36 [2]  |
| Method                                  | Repeated measure ANCOVA                                       |
| Parameter estimate                      | Difference of Least-Square Means                              |
| Point estimate                          | 0.35  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -0.401  |
| upper limit                             | 1.104   |
| Variability estimate                    | Standard error of the mean                                    |
| Dispersion value                        | 0.38  |

Notes:

[2] - Significant difference at 5% significance level.

**Secondary: Change from Baseline Over Time In the New York Heart Association (NYHA) Scores at Week 6**

|                 |  |
|-----------------|--|
| End point title | Change from Baseline Over Time In the New York Heart Association (NYHA) Scores at Week 6 |
|-----------------|--|

End point description:

Chronic Heart Failure (CHF) severity was determined by blinded study physicians using the NYHA functional classification system which relates symptoms to everyday activities and the subject's Quality of life (QoL). Whenever possible, assessment of NYHA was performed by the same site physician at each visit and for all subjects at the site.

Values missing due to subjects who died were imputed using the worst possible assessment of Class V, and subjects hospitalised during the planned assessment were attributed a value of Class IV. If a subject was alive and not hospitalised, no imputation was done for missing values.

The analysis of change in NYHA scores over time is a single analysis that includes together the analysis from BL to week 6, 12, 24. As it is not possible to represent it in EudraCT as an unique end point (single analysis model), it has been populated separately for every time point (week).

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

End point timeframe:

From Baseline to Week 6

| End point values                     | Full analysis set (FAS) - FCM | Full analysis set (FAS) - SoC |  |  |
|--------------------------------------|-------------------------------|-------------------------------|--|--|
| Subject group type                   | Subject analysis set          | Subject analysis set          |  |  |
| Number of subjects analysed          | 78                            | 78                            |  |  |
| Units: subjects                      |                               |                               |  |  |
| Improved by 2 NYHA Classes           | 0                             | 0                             |  |  |
| Improved by 1 NYHA Class             | 14                            | 5                             |  |  |
| Worsened by 1 NYHA Class             | 2                             | 2                             |  |  |
| Worsened by >1 NYHA Class            | 3                             | 2                             |  |  |
| Death (included in a category above) | 0                             | 1                             |  |  |

|           |    |    |  |  |
|-----------|----|----|--|--|
| Unchanged | 59 | 69 |  |  |
|-----------|----|----|--|--|

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | NYHA Class Change Over Time at Week 6                         |
| Statistical analysis description:   |   |
| The change in NYHA classification at each time point was analysed using repeated measures polytomous regression as described for non-continuous variables. Treatment, visit, gender, age, pooled country, BL score, and Hb level at screening (<12 g/dl or ≥12 g/dl) were included as covariates in the model; a term of interaction between visit and treatment was also included. |   |
| Comparison groups   | Full analysis set (FAS) - FCM v Full analysis set (FAS) - SoC |
| Number of subjects included in analysis   | 156   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | = 0.0215 [3]  |
| Method  | repeated measures polytomous regression                       |
| Parameter estimate  | Odds ratio (OR)   |
| Point estimate  | 2.49  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 1.144   |
| upper limit   | 5.416   |

Notes:

[3] - Significant difference at 5% significance level.

## Secondary: Change from Baseline Over Time In the New York Heart Association (NYHA) Scores at Week 12

|   |   |
|---|---|
| End point title   | Change from Baseline Over Time In the New York Heart Association (NYHA) Scores at Week 12 |
| End point description:  |   |
| Chronic Heart Failure (CHF) severity was determined by blinded study physicians using the NYHA functional classification system which relates symptoms to everyday activities and the subject's Quality of life (QoL). Whenever possible, assessment of NYHA was performed by the same site physician at each visit and for all subjects at the site. |   |
| Values missing due to subjects who died were imputed using the worst possible assessment of Class V, and subjects hospitalised during the planned assessment were attributed a value of Class IV. If a subject was alive and not hospitalised, no imputation was done for missing values.   |   |
| The analysis of change in NYHA scores over time is a single analysis that includes together the analysis from BL to week 6, 12, 24. As it is not possible to represent it in EudraCT as an unique end point (single analysis model), it has been populated separately for every time point (week).  |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| From Baseline to Week 12  |   |

| End point values                     | Full analysis set (FAS) - FCM | Full analysis set (FAS) - SoC |  |  |
|--------------------------------------|-------------------------------|-------------------------------|--|--|
| Subject group type                   | Subject analysis set          | Subject analysis set          |  |  |
| Number of subjects analysed          | 76                            | 76                            |  |  |
| Units: subjects                      |                               |                               |  |  |
| Improved by 2 NYHA Classes           | 0                             | 0                             |  |  |
| Improved by 1 NYHA Class             | 11                            | 6                             |  |  |
| Worsened by 1 NYHA Class             | 2                             | 4                             |  |  |
| Worsened by >1 NYHA Class            | 2                             | 4                             |  |  |
| Death (included in a category above) | 0                             | 2                             |  |  |
| Unchanged                            | 61                            | 62                            |  |  |

## Statistical analyses

| Statistical analysis title  | NYHA Classification Over Time at Week 12                      |
|---|---|
| Statistical analysis description:   |   |
| The change in NYHA classification at each time point was analysed using repeated measures polytomous regression as described for non-continuous variables. Treatment, visit, gender, age, pooled country, BL score, and Hb level at screening (<12 g/dl or ≥12 g/dl) were included as covariates in the model; a term of interaction between visit and treatment was also included. |   |
| Comparison groups   | Full analysis set (FAS) - FCM v Full analysis set (FAS) - SoC |
| Number of subjects included in analysis   | 152   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | = 0.0281 [4]  |
| Method  | repeated measures polytomous regression                       |
| Parameter estimate  | Odds ratio (OR)   |
| Point estimate  | 2.45  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 1.101   |
| upper limit   | 5.45  |

Notes:

[4] - Significant difference at 5% significance level.

## Secondary: Change from Baseline Over Time In the New York Heart Association (NYHA) Scores at Week 24

| End point title   | Change from Baseline Over Time In the New York Heart Association (NYHA) Scores at Week 24 |
|---|---|
| End point description:  |   |
| Chronic Heart Failure (CHF) severity was determined by blinded study physicians using the NYHA functional classification system which relates symptoms to everyday activities and the subject's Quality of life (QoL). Whenever possible, assessment of NYHA was performed by the same site physician at each visit and for all subjects at the site. |   |
| Values missing due to subjects who died were imputed using the worst possible assessment of Class V, and subjects hospitalised during the planned assessment were attributed a value of Class IV. If a subject was alive and not hospitalised, no imputation was done for missing values.   |   |
| The analysis of change in NYHA scores over time is a single analysis that includes together the analysis from BL to week 6, 12, 24. As it is not possible to represent it in EudraCT as an unique end point (single analysis model), it has been populated separately for every time point (week).  |   |
| End point type  | Secondary   |

End point timeframe:  
From Baseline to Week 24

| <b>End point values</b>              | Full analysis set (FAS) - FCM | Full analysis set (FAS) - SoC |  |  |
|--------------------------------------|-------------------------------|-------------------------------|--|--|
| Subject group type                   | Subject analysis set          | Subject analysis set          |  |  |
| Number of subjects analysed          | 74                            | 79                            |  |  |
| Units: subjects                      |                               |                               |  |  |
| Improved by 2 NYHA Classes           | 0                             | 1                             |  |  |
| Improved by 1 NYHA Class             | 12                            | 7                             |  |  |
| Worsened by 1 NYHA Class             | 1                             | 3                             |  |  |
| Worsened by >1 NYHA Class            | 0                             | 7                             |  |  |
| Death (included in a category above) | 0                             | 4                             |  |  |
| Unchanged                            | 61                            | 61                            |  |  |

## Statistical analyses

| <b>Statistical analysis title</b> | NYHA Classification Over Time at Week 24 |
|-----------------------------------|--|
|-----------------------------------|--|

Statistical analysis description:

The change in NYHA classification at each time point was analysed using repeated measures polytomous regression as described for non-continuous variables. Treatment, visit, gender, age, pooled country, BL score, and Hb level at screening (<12 g/dl or ≥12 g/dl) were included as covariates in the model; a term of interaction between visit and treatment was also included.

|   |   |
|---|---|
| Comparison groups                       | Full analysis set (FAS) - FCM v Full analysis set (FAS) - SoC |
| Number of subjects included in analysis | 153   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.001 <sup>[5]</sup>  |
| Method                                  | repeated measures polytomous regression                       |
| Parameter estimate                      | Odds ratio (OR)   |
| Point estimate                          | 3.84  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 1.719   |
| upper limit                             | 8.584   |

Notes:

[5] - Significant difference at 5% significance level.

## Secondary: Change from Baseline Over Time In the New York Heart Association (NYHA) Scores at Week 24 (LOCF)

|                 |  |
|-----------------|--|
| End point title | Change from Baseline Over Time In the New York Heart Association (NYHA) Scores at Week 24 (LOCF) |
|-----------------|--|

End point description:

Chronic Heart Failure (CHF) severity was determined by blinded study physicians using the NYHA functional classification system which relates symptoms to everyday activities and the subject's Quality of life (QoL). Whenever possible, assessment of NYHA was performed by the same site physician at each visit and for all subjects at the site.

Values missing due to subjects who died were imputed using the worst possible assessment of Class V, and subjects hospitalised during the planned assessment were attributed a value of Class IV. If a subject was alive and not hospitalised, no imputation was done for missing values.

|                      |   |
|----------------------|---|
| End point type       | Secondary   |
| End point timeframe: | From Baseline to Week 24 (LOCF) is the last non-missing post-baseline value on or before Week 24. |

| End point values                     | Full analysis set (FAS) - FCM | Full analysis set (FAS) - SoC |  |  |
|--------------------------------------|-------------------------------|-------------------------------|--|--|
| Subject group type                   | Subject analysis set          | Subject analysis set          |  |  |
| Number of subjects analysed          | 86                            | 86                            |  |  |
| Units: subjects                      |                               |                               |  |  |
| Improved by 2 NYHA Classes           | 0                             | 1                             |  |  |
| Improved by 1 NYHA Class             | 15                            | 7                             |  |  |
| Worsened by 1 NYHA Class             | 2                             | 4                             |  |  |
| Worsened by >1 NYHA Class            | 4                             | 5                             |  |  |
| Death (included in a category above) | 0                             | 4                             |  |  |
| Unchanged                            | 65                            | 69                            |  |  |

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | NYHA Classification Over Time at Week 24 (LOCF) |
|-----------------------------------|---|

Statistical analysis description:

The change in NYHA classification at Week 24 (LOCF) point was analysed using logistic regression as described for non-continuous variables. Treatment, gender, age, pooled country, BL score, and Hb level at screening (<12 g/dl or ≥12 g/dl) were included as covariates in the model.

|   |   |
|---|---|
| Comparison groups                       | Full analysis set (FAS) - FCM v Full analysis set (FAS) - SoC |
| Number of subjects included in analysis | 172   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.044   |
| Method                                  | Regression, Logistic  |
| Parameter estimate                      | Odds ratio (OR)   |
| Point estimate                          | 2.18  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 1.021   |
| upper limit                             | 4.651   |

## Secondary: Patient Global Assessment (PGA) At Week 6

|                 |   |
|-----------------|---|
| End point title | Patient Global Assessment (PGA) At Week 6 |
|-----------------|---|

End point description:

The PGA, which was translated in the local language, asked subjects to rate the change in their medical

condition since the start of the study as follows: "has much improved", "has (moderately) improved", "has a little improved", "is unchanged", "is a little worse", "is (moderately) worse" or "is much worse".

Questionnaires were completed before any other procedures at each visit.

Missing PGA values due to death were imputed as "died" and missing PGA values due to hospitalisation were imputed as "much worse."

The analysis of PGA over time is a single analysis that includes together the analysis at week 6, 12, 24 and 24(LOCF). As it is not possible to represent it in EudraCT as an unique end point (single analysis model), it has been populated separately for every time point (week).

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 6               |           |

| End point values            | Full analysis set (FAS) - FCM | Full analysis set (FAS) - SoC |  |  |
|-----------------------------|-------------------------------|-------------------------------|--|--|
| Subject group type          | Subject analysis set          | Subject analysis set          |  |  |
| Number of subjects analysed | 76                            | 76                            |  |  |
| Units: subjects             |                               |                               |  |  |
| Has much improved           | 3                             | 5                             |  |  |
| Has (moderately) improved   | 16                            | 12                            |  |  |
| Has a little improved       | 16                            | 14                            |  |  |
| Is unchanged                | 35                            | 34                            |  |  |
| Is a little worse           | 2                             | 5                             |  |  |
| Is (moderately) worse       | 0                             | 2                             |  |  |
| Is much worse               | 4                             | 3                             |  |  |
| Died                        | 0                             | 1                             |  |  |

## Statistical analyses

|                            |            |
|----------------------------|------------|
| Statistical analysis title | PGA Week 6 |
|----------------------------|------------|

Statistical analysis description:

Results at each time point are from a repeated measures polytomous model including treatment, visit, gender, age, pooled country, haemoglobin level at screening (<12 g/dL, ≥12 g/dL), as well as interaction between visit and treatment.

Wald 95% CI are offered below.

|   |   |
|---|---|
| Comparison groups                       | Full analysis set (FAS) - FCM v Full analysis set (FAS) - SoC |
| Number of subjects included in analysis | 152   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.43  |
| Method                                  | repeated measures polytomous model                            |
| Parameter estimate                      | Odds ratio (OR)   |
| Point estimate                          | 1.3   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.71  |
| upper limit                             | 2.27  |

## Secondary: Patient Global Assessment (PGA) At Week 12

|                        |   |
|------------------------|---|
| End point title        | Patient Global Assessment (PGA) At Week 12  |
| End point description: | <p>The PGA, which was translated in the local language, asked subjects to rate the change in their medical condition since the start of the study as follows: "has much improved", "has (moderately) improved", "has a little improved", "is unchanged", "is a little worse", "is (moderately) worse" or "is much worse". Questionnaires were completed before any other procedures at each visit.</p> <p>Missing PGA values due to death were imputed as "died" and missing PGA values due to hospitalisation were imputed as "much worse."</p> <p>The analysis of PGA over time is a single analysis that includes together the analysis at week 6, 12, 24 and 24(LOCF). As it is not possible to represent it in EudraCT as an unique end point (single analysis model), it has been populated separately for every time point (week).</p> |
| End point type         | Secondary   |
| End point timeframe:   | Week 12   |

| End point values            | Full analysis set (FAS) - FCM | Full analysis set (FAS) - SoC |  |  |
|-----------------------------|-------------------------------|-------------------------------|--|--|
| Subject group type          | Subject analysis set          | Subject analysis set          |  |  |
| Number of subjects analysed | 75                            | 76                            |  |  |
| Units: subjects             |                               |                               |  |  |
| Has much improved           | 6                             | 4                             |  |  |
| Has (moderately) improved   | 15                            | 7                             |  |  |
| Has a little improved       | 27                            | 19                            |  |  |
| Is unchanged                | 20                            | 33                            |  |  |
| Is a little worse           | 3                             | 6                             |  |  |
| Is (moderately) worse       | 0                             | 1                             |  |  |
| Is much worse               | 4                             | 4                             |  |  |
| Died                        | 0                             | 2                             |  |  |

## Statistical analyses

|                                   |  |
|-----------------------------------|--|
| Statistical analysis title        | PGA Week 12  |
| Statistical analysis description: | <p>Results at each time point are from a repeated measures polytomous model including treatment, visit, gender, age, pooled country, haemoglobin level at screening (&lt;12 g/dL, ≥12 g/dL), as well as interaction between visit and treatment.</p> <p>Wald 95% CI are offered below.</p> |
| Comparison groups                 | Full analysis set (FAS) - FCM v Full analysis set (FAS) - SoC  |

|   |                                    |
|---|------------------------------------|
| Number of subjects included in analysis | 151                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority                        |
| P-value                                 | = 0.0055 [6]                       |
| Method                                  | repeated measures polytomous model |
| Parameter estimate                      | Odds ratio (OR)                    |
| Point estimate                          | 2.3                                |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | 1.27                               |
| upper limit                             | 4.02                               |

Notes:

[6] - Analysis performed using 2-sided tests at the 5% significance level.

### Secondary: Patient Global Assessment (PGA) At Week 24

|                 |  |
|-----------------|--|
| End point title | Patient Global Assessment (PGA) At Week 24 |
|-----------------|--|

End point description:

The PGA, which was translated in the local language, asked subjects to rate the change in their medical condition since the start of the study as follows: "has much improved", "has (moderately) improved", "has a little improved", "is unchanged", "is a little worse", "is (moderately) worse" or "is much worse". Questionnaires were completed before any other procedures at each visit.

Missing PGA values due to death were imputed as "died" and missing PGA values due to hospitalisation were imputed as "much worse."

The analysis of PGA over time is a single analysis that includes together the analysis at week 6, 12, 24 and 24 (LOCF). As it is not possible to represent it in EudraCT as an unique end point (single analysis model), it has been populated separately for every time point (week).

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

End point timeframe:

Week 24

| End point values            | Full analysis set (FAS) - FCM | Full analysis set (FAS) - SoC |  |  |
|-----------------------------|-------------------------------|-------------------------------|--|--|
| Subject group type          | Subject analysis set          | Subject analysis set          |  |  |
| Number of subjects analysed | 73                            | 80                            |  |  |
| Units: subjects             |                               |                               |  |  |
| Has much improved           | 8                             | 5                             |  |  |
| Has (moderately) improved   | 16                            | 11                            |  |  |
| Has a little improved       | 27                            | 16                            |  |  |
| Is unchanged                | 17                            | 32                            |  |  |
| Is a little worse           | 3                             | 8                             |  |  |
| Is (moderately) worse       | 1                             | 2                             |  |  |
| Is much worse               | 1                             | 2                             |  |  |
| Died                        | 0                             | 4                             |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | PGA Week 24   |
| Statistical analysis description:   |   |
| Results at each time point are from a repeated measures polytomous model including treatment, visit, gender, age, pooled country, haemoglobin level at screening (<12 g/dL, ≥12 g/dL), as well as interaction between visit and treatment. Wald 95% CI are offered below. |   |
| Comparison groups   | Full analysis set (FAS) - FCM v Full analysis set (FAS) - SoC |
| Number of subjects included in analysis   | 153   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | = 0.0004 [7]  |
| Method  | repeated measures polytomous model                            |
| Parameter estimate  | Odds ratio (OR)   |
| Point estimate  | 2.9   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 1.6   |
| upper limit   | 5.23  |

Notes:

[7] - Analysis performed using 2-sided tests at the 5% significance level.

### Secondary: Patient Global Assessment (PGA) At Week 24 (LOCF)

|  |   |
|--|---|
| End point title  | Patient Global Assessment (PGA) At Week 24 (LOCF) |
| End point description:   |   |
| The PGA, which was translated in the local language, asked subjects to rate the change in their medical condition since the start of the study as follows: "has much improved", "has (moderately) improved", "has a little improved", "is unchanged", "is a little worse", "is (moderately) worse" or "is much worse". Questionnaires were completed before any other procedures at each visit. Missing PGA values due to death were imputed as "died" and missing PGA values due to hospitalisation were imputed as "much worse." |   |
| Week 24 (LOCF) is the last non-missing post baseline value on or before week 24.   |   |
| The analysis of PGA over time is a single analysis that includes together the analysis at week 6, 12, 24 and 24 (LOCF). As it is not possible to represent it in EudraCT as an unique end point (single analysis model), it has been populated separately for every time point (week).   |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Week 24 (LOCF)   |   |

| End point values            | Full analysis set (FAS) - FCM | Full analysis set (FAS) - SoC |  |  |
|-----------------------------|-------------------------------|-------------------------------|--|--|
| Subject group type          | Subject analysis set          | Subject analysis set          |  |  |
| Number of subjects analysed | 86                            | 86                            |  |  |
| Units: subjects             |                               |                               |  |  |
| Has much improved           | 9                             | 5                             |  |  |
| Has (moderately) improved   | 17                            | 11                            |  |  |
| Has a little improved       | 30                            | 17                            |  |  |
| Is unchanged                | 20                            | 37                            |  |  |
| Is a little worse           | 4                             | 8                             |  |  |
| Is (moderately) worse       | 1                             | 4                             |  |  |
| Is much worse               | 5                             | 0                             |  |  |

|      |   |   |  |  |
|------|---|---|--|--|
| Died | 0 | 4 |  |  |
|------|---|---|--|--|

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Week 24 (LOCF)  |
| Statistical analysis description:  |   |
| At Week 24 (LOCF), PGA was analysed with a logistic regression including the same covariates as described for non-continuous variables. Treatment, gender, age, pooled country, and Hb level at screening (<12 g/dl or ≥12 g/dl) were included as covariates in the model. |   |
| Comparison groups  | Full analysis set (FAS) - FCM v Full analysis set (FAS) - SoC |
| Number of subjects included in analysis  | 172   |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | = 0.0038 <sup>[8]</sup>                                       |
| Method   | Polytomous regression   |
| Parameter estimate   | Odds ratio (OR)   |
| Point estimate   | 2.3   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 1.31  |
| upper limit  | 4   |

Notes:

[8] - Significant difference at 5% significance level.

## Secondary: Hospitalisation rate

|  |                      |
|--|----------------------|
| End point title  | Hospitalisation rate |
| End point description:   |                      |
| Hospitalisation rate is computed as number of patients experiencing adverse events leading to hospitalisation divided by the number of patients in that treatment group. |                      |
| End point type   | Secondary            |
| End point timeframe:   |                      |
| From Baseline until Week 24  |                      |

| End point values                          | Safety Set (SS)<br>- FCM | Safety Set (SS)<br>- SoC |  |  |
|---|--------------------------|--------------------------|--|--|
| Subject group type                        | Subject analysis set     | Subject analysis set     |  |  |
| Number of subjects analysed               | 88                       | 85                       |  |  |
| Units: Percent                            |                          |                          |  |  |
| number (not applicable)                   |                          |                          |  |  |
| Any hospitalisation                       | 30.7                     | 15.3                     |  |  |
| Due to worsening of CHF                   | 12.5                     | 7.1                      |  |  |
| Due to other cardiovascular related event | 13.6                     | 3.5                      |  |  |
| Due to a non-cardiovascular event         | 10.2                     | 4.7                      |  |  |

|                                 |   |     |  |  |
|---------------------------------|---|-----|--|--|
| Due to a serious drug reaction  | 0 | 0   |  |  |
| Other                           | 0 | 0   |  |  |
| Insufficient data to adjudicate | 0 | 1.2 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Death rate

|                 |            |
|-----------------|------------|
| End point title | Death rate |
|-----------------|------------|

End point description:

Death rate is computed as number of patients experiencing adverse events leading to death divided by the number of patients in that treatment group.

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

End point timeframe:

From Baseline until Week 24

| End point values                          | Safety Set (SS)<br>- FCM | Safety Set (SS)<br>- SoC |  |  |
|---|--------------------------|--------------------------|--|--|
| Subject group type                        | Subject analysis set     | Subject analysis set     |  |  |
| Number of subjects analysed               | 88                       | 85                       |  |  |
| Units: percent                            |                          |                          |  |  |
| number (not applicable)                   |                          |                          |  |  |
| Any death                                 | 0                        | 5.9                      |  |  |
| Due to worsening of CHF                   | 0                        | 1.2                      |  |  |
| Due to other cardiovascular related event | 0                        | 2.4                      |  |  |
| Due to a non-cardiovascular event         | 0                        | 1.2                      |  |  |
| Due to a serious drug reaction            | 0                        | 0                        |  |  |
| Other                                     | 0                        | 0                        |  |  |
| Insufficient data to adjudicate           | 0                        | 1.2                      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to First Hospitalisation or Death for Worsening of Chronic Heart Failure (CHF)

|                 |   |
|-----------------|---|
| End point title | Time to First Hospitalisation or Death for Worsening of Chronic Heart Failure (CHF) |
|-----------------|---|

End point description:

Time-to-event analyses for hospitalisation and for death (as well as incidence of hospitalisations and deaths) were based on adjudicated events and were analysed for the SS. Qualification of events as "worsening of CHF" event was determined by an independent and blinded committee that reviewed all deaths and unplanned hospitalisations. For each reason, the incidence rate ratios of the number of recurrent events between treatment groups and its relative 95% confidence interval (CI) and p-values were calculated using a negative binomial regression including total study duration (calculated from BL

to Week 24 (LOCF)) as covariate.

Number of subjects with at least one event is 11 (12.5%) for the FCM group and 6 (7.1%) for the SoC group.

|  |           |
|--|-----------|
| End point type                           | Secondary |
| End point timeframe:                     |           |
| Before Week 6, Week 12, Week 18, Week 24 |           |

| End point values   | Safety Set (SS)<br>- FCM | Safety Set (SS)<br>- SoC |  |  |
|--|--------------------------|--------------------------|--|--|
| Subject group type   | Subject analysis set     | Subject analysis set     |  |  |
| Number of subjects analysed  | 88                       | 85                       |  |  |
| Units: estimated probability of events<br>number (confidence interval 95%) |                          |                          |  |  |
| Before 6 weeks (day 43)  | 0.05 (0.017 to<br>0.117) | 0.04 (0.012 to<br>0.107) |  |  |
| Before 12 week (day 85)  | 0.09 (0.047 to<br>0.174) | 0.05 (0.018 to<br>0.122) |  |  |
| Before 18 weeks (day 127)  | 0.1 (0.055 to<br>0.187)  | 0.06 (0.025 to<br>0.138) |  |  |
| Before 24 weeks (day 169)  | 0.13 (0.072 to<br>0.216) | 0.07 (0.033 to<br>0.154) |  |  |
| Maximum time   | 0.13 (0.072 to<br>0.216) | 0.07 (0.033 to<br>0.154) |  |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Hospitalisation or Death due to Worsening of CHF |
| Comparison groups                       | Safety Set (SS) - FCM v Safety Set (SS) - SoC    |
| Number of subjects included in analysis | 173  |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | = 0.26   |
| Method                                  | Logrank  |
| Parameter estimate                      | Hazard ratio (HR)                                |
| Point estimate                          | 1.76   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.67   |
| upper limit                             | 5.114  |

### Secondary: Time to First Hospitalisation or Death for Worsening of CHF or Other Cardiovascular Related (CV) Events

|                        |   |
|------------------------|---|
| End point title        | Time to First Hospitalisation or Death for Worsening of CHF or Other Cardiovascular Related (CV) Events |
| End point description: |   |

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

End point timeframe:

Before Week 6, Week 12, Week 18, Week 24, Maximum time

| <b>End point values</b>                | Safety Set (SS)<br>- FCM | Safety Set (SS)<br>- SoC |  |  |
|--|--------------------------|--------------------------|--|--|
| Subject group type                     | Subject analysis set     | Subject analysis set     |  |  |
| Number of subjects analysed            | 88                       | 85                       |  |  |
| Units: estimated probability of events |                          |                          |  |  |
| number (confidence interval 95%)       |                          |                          |  |  |
| Before 6 weeks (day 43)                | 0.08 (0.039 to 0.16)     | 0.05 (0.018 to 0.121)    |  |  |
| Before 12 weeks (day 85)               | 0.17 (0.106 to 0.267)    | 0.06 (0.025 to 0.136)    |  |  |
| Before 18 weeks (day 127)              | 0.22 (0.144 to 0.318)    | 0.08 (0.04 to 0.166)     |  |  |
| Before 24 weeks (day 169)              | 0.25 (0.173 to 0.356)    | 0.12 (0.066 to 0.21)     |  |  |
| Maximum time                           | 0.25 (0.173 to 0.356)    | 0.15 (0.082 to 0.279)    |  |  |

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Hospitalisation/Death for Worsening of CHF and CV |
|-----------------------------------|---|

Statistical analysis description:

Time to First Hospitalisation or Death for Worsening of CHF or Other Cardiovascular Related (CV) Events. 95% CI (confidence interval) for the estimated probability are derived using Greenwood formula. The hazard ratio and associated 95% CI (confidence interval) are calculated from the proportional hazards model.

|   |   |
|---|---|
| Comparison groups                       | Safety Set (SS) - FCM v Safety Set (SS) - SoC |
| Number of subjects included in analysis | 173   |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | superiority                                   |
| P-value                                 | = 0.0442 [9]                                  |
| Method                                  | Logrank                                       |
| Parameter estimate                      | Hazard ratio (HR)                             |
| Point estimate                          | 2.07  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided                                       |
| lower limit                             | 1.024   |
| upper limit                             | 4.43  |

Notes:

[9] - Significant difference at 5% significance level.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the time the subjects signed the Informed Consent Form. The Adverse Event (AE) reporting ended on the last study visit (Week 24). AEs spontaneously reported within 30 days after the last study visit were included in the safety analyses.

Adverse event reporting additional description:

Only Treatment Emergent Adverse Event are reported.

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Ferric carboxymaltose |
|-----------------------|-----------------------|

Reporting group description:

subjects that received FCM

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Standard of Care |
|-----------------------|------------------|

Reporting group description:

Subjects randomised to SoC were permitted to receive oral iron at the Investigator's discretion; however, IV iron was not permitted

| <b>Serious adverse events</b>                                       | Ferric carboxymaltose | Standard of Care |  |
|---|-----------------------|------------------|--|
| Total subjects affected by serious adverse events                   |                       |                  |  |
| subjects affected / exposed   | 28 / 88 (31.82%)      | 16 / 85 (18.82%) |  |
| number of deaths (all causes)                                       | 0                     | 5                |  |
| number of deaths resulting from adverse events                      | 0                     | 0                |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                       |                  |  |
| Adenocarcinoma gastric  |                       |                  |  |
| subjects affected / exposed   | 1 / 88 (1.14%)        | 0 / 85 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1                 | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0                 | 0 / 0            |  |
| Vascular disorders  |                       |                  |  |
| Deep vein thrombosis  |                       |                  |  |
| subjects affected / exposed   | 0 / 88 (0.00%)        | 1 / 85 (1.18%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0                 | 0 / 1            |  |
| deaths causally related to treatment / all                          | 0 / 0                 | 0 / 0            |  |
| Thrombosis  |                       |                  |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                                 | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          |  |
| <b>General disorders and administration site conditions</b> |                |                |  |
| Implant site inflammation                                   |                |                |  |
| subjects affected / exposed                                 | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          |  |
| <b>Non-cardiac chest pain</b>                               |                |                |  |
| subjects affected / exposed                                 | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          |  |
| <b>Sudden cardiac death</b>                                 |                |                |  |
| subjects affected / exposed                                 | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 1          |  |
| <b>Sudden death</b>   |                |                |  |
| subjects affected / exposed                                 | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 1          |  |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |                |                |  |
| Acute pulmonary oedema                                      |                |                |  |
| subjects affected / exposed                                 | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          |  |
| Acute respiratory failure                                   |                |                |  |
| subjects affected / exposed                                 | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 1          |  |
| Chronic obstructive pulmonary disease                       |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                           | 2 / 88 (2.27%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          |  |
| <b>Respiratory failure</b>                            |                |                |  |
| subjects affected / exposed                           | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          |  |
| <b>Product issues</b>                                 |                |                |  |
| <b>Device battery issue</b>                           |                |                |  |
| subjects affected / exposed                           | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          |  |
| <b>Device malfunction</b>                             |                |                |  |
| subjects affected / exposed                           | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          |  |
| <b>Injury, poisoning and procedural complications</b> |                |                |  |
| <b>Tibia fracture</b>                                 |                |                |  |
| subjects affected / exposed                           | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          |  |
| <b>Cardiac disorders</b>                              |                |                |  |
| <b>Acute myocardial infarction</b>                    |                |                |  |
| subjects affected / exposed                           | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          |  |
| <b>Angina pectoris</b>                                |                |                |  |
| subjects affected / exposed                           | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          |  |
| <b>Atrial fibrillation</b>                            |                |                |  |
| subjects affected / exposed                           | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Atrial flutter                                  |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac arrest                                  |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac asthma                                  |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac failure                                 |                |                |  |
| subjects affected / exposed                     | 6 / 88 (6.82%) | 4 / 85 (4.71%) |  |
| occurrences causally related to treatment / all | 0 / 6          | 0 / 9          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Cardiac failure chronic                         |                |                |  |
| subjects affected / exposed                     | 4 / 88 (4.55%) | 2 / 85 (2.35%) |  |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 4          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Left ventricular dysfunction                    |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Myocardial ischaemia                            |                |                |  |
| subjects affected / exposed                     | 2 / 88 (2.27%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ventricular fibrillation                        |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ventricular tachycardia                         |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Nervous system disorders</b>                 |                |                |  |
| Cerebrovascular accident                        |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| 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                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Gastrointestinal disorders</b>               |                |                |  |
| Abdominal pain                                  |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastric ulcer haemorrhage                       |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vomiting  |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Hepatobiliary disorders</b>                  |                |                |  |
| Bile duct stenosis                              |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bile duct stone                                 |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Renal and urinary disorders                     |                |                |  |
| Acute kidney injury                             |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal failure                                   |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (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                     |                |                |  |
| Endocarditis                                    |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Intervertebral discitis                         |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 3 / 88 (3.41%) | 2 / 85 (2.35%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia influenzal                            |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Sepsis  |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Upper respiratory tract infection               |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Uterine infection                               |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |
| Diabetes mellitus                               |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypercalcaemia                                  |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypocalcaemia                                   |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (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: 0 %

| <b>Non-serious adverse events</b>                                   | Ferric carboxymaltose | Standard of Care |  |
|---|-----------------------|------------------|--|
| Total subjects affected by non-serious adverse events               |                       |                  |  |
| subjects affected / exposed   | 54 / 88 (61.36%)      | 35 / 85 (41.18%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                       |                  |  |
| Basal cell carcinoma  |                       |                  |  |
| subjects affected / exposed   | 0 / 88 (0.00%)        | 1 / 85 (1.18%)   |  |
| occurrences (all)   | 0                     | 1                |  |
| Vascular disorders  |                       |                  |  |
| Hypertension  |                       |                  |  |
| subjects affected / exposed   | 0 / 88 (0.00%)        | 1 / 85 (1.18%)   |  |
| occurrences (all)   | 0                     | 1                |  |
| Hypotension   |                       |                  |  |
| subjects affected / exposed   | 0 / 88 (0.00%)        | 1 / 85 (1.18%)   |  |
| occurrences (all)   | 0                     | 1                |  |
| General disorders and administration site conditions                |                       |                  |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Asthenia  |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 2 / 85 (2.35%) |  |
| occurrences (all)                               | 1              | 2              |  |
| Implant site inflammation                       |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Influenza like illness                          |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 85 (2.35%) |  |
| occurrences (all)                               | 0              | 2              |  |
| Malaise   |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Necrosis  |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Non-cardiac chest pain                          |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Oedema  |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Oedema peripheral                               |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Puncture site reaction                          |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Pyrexia   |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Bronchitis chronic                              |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 1 / 85 (1.18%) |  |
| occurrences (all)                               | 1              | 1              |  |
| Cough   |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Dyspnoea  |                |                |  |
| subjects affected / exposed                     | 2 / 88 (2.27%) | 3 / 85 (3.53%) |  |
| occurrences (all)                               | 2              | 3              |  |
| Dyspnoea exertional                             |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Pulmonary oedema                                |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Respiratory failure                             |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Investigations                                  |                |                |  |
| Blood creatine increased                        |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Blood glucose decreased                         |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Blood glucose increased                         |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Blood pressure decreased                        |                |                |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Haemodynamic test                               |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences (all)                               | 0              | 1              |  |
| N-terminal prohormone brain natriuretic peptide |                |                |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Urine output decreased                          |                |                |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                                 | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Volume blood decreased<br>subjects affected / exposed<br>occurrences (all)       | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)             | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Injury, poisoning and procedural complications                                   |                     |                     |  |
| Accidental overdose<br>subjects affected / exposed<br>occurrences (all)          | 3 / 88 (3.41%)<br>3 | 0 / 85 (0.00%)<br>0 |  |
| Alcohol poisoning<br>subjects affected / exposed<br>occurrences (all)            | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 88 (0.00%)<br>0 | 2 / 85 (2.35%)<br>2 |  |
| Drug dose omission<br>subjects affected / exposed<br>occurrences (all)           | 3 / 88 (3.41%)<br>3 | 0 / 85 (0.00%)<br>0 |  |
| Expired product administered<br>subjects affected / exposed<br>occurrences (all) | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                         | 3 / 88 (3.41%)<br>3 | 1 / 85 (1.18%)<br>1 |  |
| Fat embolism<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Incorrect drug administration<br>duration  |                     |                     |  |

|                                    |                |                |  |
|------------------------------------|----------------|----------------|--|
| subjects affected / exposed        | 6 / 88 (6.82%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 6              | 0              |  |
| Incorrect drug administration rate |                |                |  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Ligament sprain                    |                |                |  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Procedural dizziness               |                |                |  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Product preparation error          |                |                |  |
| subjects affected / exposed        | 6 / 88 (6.82%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 6              | 0              |  |
| Cardiac disorders                  |                |                |  |
| Angina pectoris                    |                |                |  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Atrial fibrillation                |                |                |  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Atrial flutter                     |                |                |  |
| subjects affected / exposed        | 2 / 88 (2.27%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 2              | 0              |  |
| Atrial thrombosis                  |                |                |  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Atrioventricular block             |                |                |  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Cardiac failure                    |                |                |  |
| subjects affected / exposed        | 3 / 88 (3.41%) | 6 / 85 (7.06%) |  |
| occurrences (all)                  | 4              | 6              |  |
| Cardiac failure chronic            |                |                |  |
| subjects affected / exposed        | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences (all)                  | 0              | 1              |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| Coronary artery stenosis<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Left ventricular dysfunction<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Nodal rhythm<br>subjects affected / exposed<br>occurrences (all)   | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)   | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Sinus bradycardia<br>subjects affected / exposed<br>occurrences (all)  | 2 / 88 (2.27%)<br>2 | 0 / 85 (0.00%)<br>0 |  |
| Ventricular arrhythmia<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Ventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Ventricular fibrillation<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Ventricular tachycardia<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 88 (1.14%)<br>1 | 1 / 85 (1.18%)<br>1 |  |
| Nervous system disorders<br>Cerebrovascular accident<br>subjects affected / exposed<br>occurrences (all)       | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Blood and lymphatic system disorders<br>Anaemia macrocytic<br>subjects affected / exposed<br>occurrences (all) | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Antiphospholipid syndrome  |                     |                     |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Hypocoagulable state<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Ear and labyrinth disorders<br>Ear discomfort<br>subjects affected / exposed<br>occurrences (all)      | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)  | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Eye disorders<br>Cataract<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Gastrointestinal disorders<br>Abdominal distension<br>subjects affected / exposed<br>occurrences (all) | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                                     | 2 / 88 (2.27%)<br>2 | 0 / 85 (0.00%)<br>0 |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 88 (1.14%)<br>1 | 4 / 85 (4.71%)<br>4 |  |
| Ascites<br>subjects affected / exposed<br>occurrences (all)  | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Diarrhoea  |                     |                     |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                       | 1 / 88 (1.14%)<br>1 | 1 / 85 (1.18%)<br>1 |  |
| Faeces discoloured<br>subjects affected / exposed<br>occurrences (all) | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Gastric ulcer<br>subjects affected / exposed<br>occurrences (all)      | 2 / 88 (2.27%)<br>2 | 0 / 85 (0.00%)<br>0 |  |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)          | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Gastritis erosive<br>subjects affected / exposed<br>occurrences (all)  | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)             | 2 / 88 (2.27%)<br>3 | 0 / 85 (0.00%)<br>0 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)           | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Hepatobiliary disorders  |                     |                     |  |
| Bile duct stone<br>subjects affected / exposed<br>occurrences (all)    | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Cholelithiasis<br>subjects affected / exposed<br>occurrences (all)     | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Hepatic failure<br>subjects affected / exposed<br>occurrences (all)    | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Hepatic steatosis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Skin and subcutaneous tissue disorders                                 |                     |                     |  |
| Eczema   |                     |                     |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Psoriasis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Senile pruritus<br>subjects affected / exposed<br>occurrences (all)   | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Skin ulcer<br>subjects affected / exposed<br>occurrences (all)  | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Renal and urinary disorders<br>Renal and urinary disorders<br>subjects affected / exposed<br>occurrences (all)    | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 1 / 88 (1.14%)<br>1 | 1 / 85 (1.18%)<br>1 |  |
| Arthritis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 2 / 88 (2.27%)<br>2 | 0 / 85 (0.00%)<br>0 |  |
| Dupuytren's contracture<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)   | 1 / 88 (1.14%)<br>1 | 1 / 85 (1.18%)<br>1 |  |
| Musculoskeletal pain  |                     |                     |  |

|                              |                |                |  |
|------------------------------|----------------|----------------|--|
| subjects affected / exposed  | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)            | 1              | 0              |  |
| Osteoarthritis               |                |                |  |
| subjects affected / exposed  | 0 / 88 (0.00%) | 2 / 85 (2.35%) |  |
| occurrences (all)            | 0              | 2              |  |
| Pain in extremity            |                |                |  |
| subjects affected / exposed  | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)            | 1              | 0              |  |
| Sjogren's syndrome           |                |                |  |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences (all)            | 0              | 1              |  |
| Spinal osteoarthritis        |                |                |  |
| subjects affected / exposed  | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)            | 1              | 0              |  |
| Systemic lupus erythematosus |                |                |  |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences (all)            | 0              | 1              |  |
| Infections and infestations  |                |                |  |
| Anal abscess                 |                |                |  |
| subjects affected / exposed  | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)            | 1              | 0              |  |
| Bronchitis                   |                |                |  |
| subjects affected / exposed  | 2 / 88 (2.27%) | 2 / 85 (2.35%) |  |
| occurrences (all)            | 2              | 2              |  |
| Cholecystitis infective      |                |                |  |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences (all)            | 0              | 1              |  |
| Cystitis                     |                |                |  |
| subjects affected / exposed  | 1 / 88 (1.14%) | 1 / 85 (1.18%) |  |
| occurrences (all)            | 1              | 1              |  |
| Folliculitis                 |                |                |  |
| subjects affected / exposed  | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)            | 1              | 0              |  |
| Gastroenteritis              |                |                |  |
| subjects affected / exposed  | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)            | 1              | 0              |  |

|                                    |                |                |  |
|------------------------------------|----------------|----------------|--|
| Herpes zoster                      |                |                |  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Influenza                          |                |                |  |
| subjects affected / exposed        | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Intervertebral discitis            |                |                |  |
| subjects affected / exposed        | 0 / 88 (0.00%) | 1 / 85 (1.18%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Nasopharyngitis                    |                |                |  |
| subjects affected / exposed        | 5 / 88 (5.68%) | 2 / 85 (2.35%) |  |
| occurrences (all)                  | 5              | 2              |  |
| Pharyngitis                        |                |                |  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Pneumonia                          |                |                |  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 2 / 85 (2.35%) |  |
| occurrences (all)                  | 1              | 2              |  |
| Respiratory tract infection        |                |                |  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 1 / 85 (1.18%) |  |
| occurrences (all)                  | 1              | 1              |  |
| Upper respiratory tract infection  |                |                |  |
| subjects affected / exposed        | 3 / 88 (3.41%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 3              | 0              |  |
| Urinary tract infection            |                |                |  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Metabolism and nutrition disorders |                |                |  |
| Electrolyte imbalance              |                |                |  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 0 / 85 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Gout                               |                |                |  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 1 / 85 (1.18%) |  |
| occurrences (all)                  | 1              | 1              |  |
| Hypercalcaemia                     |                |                |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                         | 1 / 88 (1.14%)<br>1 | 0 / 85 (0.00%)<br>0 |  |
| Hyperuricaemia<br>subjects affected / exposed<br>occurrences (all)       | 2 / 88 (2.27%)<br>2 | 1 / 85 (1.18%)<br>1 |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)         | 2 / 88 (2.27%)<br>2 | 2 / 85 (2.35%)<br>3 |  |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)      | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Hypophosphataemia<br>subjects affected / exposed<br>occurrences (all)    | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Iron deficiency<br>subjects affected / exposed<br>occurrences (all)      | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |
| Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all) | 0 / 88 (0.00%)<br>0 | 1 / 85 (1.18%)<br>1 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 27 March 2012    | <ul style="list-style-type: none"><li>• The dosing scheme was revised. so that for all subjects, FCM dosing on Day 1 and Week 6 was based on screening Hb and screening weight and not on serum ferritin and TSAT results from Day 1 or Week 6.</li><li>• Exclusion criterion (subject with body weight &lt;35 kg) was added to reflect updated prescribing information for FCM.</li></ul>   |
| 27 July 2012     | <ul style="list-style-type: none"><li>• introduced changes to the risks/precautions section of the protocol to clarify the risk of hypersensitivity and anaphylactoid reactions</li></ul>  |
| 06 November 2013 | <ul style="list-style-type: none"><li>• The upper limit for screening peak VO<sub>2</sub> assessments (Inclusion criterion) was increased from 18 to 20 mL/kg/min</li><li>• Exclusion Criterion (previously randomised in FER-CARS-05) was added</li><li>• Exclusion Criterion (cardio resynchronisation therapy device implantation within 6 months prior to screening) was added</li><li>• A 30-minute observation period after FCM administration was added</li><li>• Addition of Screening Visit 1 split procedure allows the option for the first screening visit (Visit 1) to be conducted on 2 separate days, in order to give the sites time to confirm that a subject meets the central laboratory test requirements for eligibility before the peak VO<sub>2</sub> assessment is performed</li><li>• Peak work rate was added as an additional secondary efficacy endpoint</li><li>• Addition of procedures for subjects with implanted cardiac rhythm management devices</li><li>• Addition of new sites to the study (due to slow recruitment)</li></ul> |
| 09 June 2014     | <ul style="list-style-type: none"><li>• Change in Cardiopulmonary exercise (CPX) test data format required for submission to the CORELAB (to accommodate sites unable to provide data in the originally specified format)</li></ul>  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported