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 (VO2).

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:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	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 VO2) were completed by an independent consultant unaware of subject treatment. All peak VO2 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
Arm title	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).

Arm title	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
Company decision (protocol violation)	1	1
Consent withdrawn by subject	2	-
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 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 Units: years			
arithmetic mean	62.7	64.4	
standard deviation	± 11.45	± 11.42	-
Gender categorical 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 Analysisi 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:

Sefety 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 VO2 (mL/kg/min) from baseline to Week 24 (LOCF)

End point title	Change in peak VO2 (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 VO2 (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)

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	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

Statistical analysis title	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

Statistical analysis title	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

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	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

Statistical analysis title	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 [5]
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

Statistical analysis title	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:

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 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:

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	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

Statistical analysis title	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

Statistical analysis title	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 [8]
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) - FCM	Safety Set (SS) - 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) - FCM	Safety Set (SS) - 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) - FCM	Safety Set (SS) - 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)	0.05 (0.017 to 0.117)	0.04 (0.012 to 0.107)		
Before 12 week (day 85)	0.09 (0.047 to 0.174)	0.05 (0.018 to 0.122)		
Before 18 weeks (day 127)	0.1 (0.055 to 0.187)	0.06 (0.025 to 0.138)		
Before 24 weeks (day 169)	0.13 (0.072 to 0.216)	0.07 (0.033 to 0.154)		
Maximum time	0.13 (0.072 to 0.216)	0.07 (0.033 to 0.154)		

Statistical analyses

Statistical analysis title	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

End point values	Safety Set (SS) - FCM	Safety Set (SS) - 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

Statistical analysis title	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

Serious adverse events	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	
General disorders and administration site conditions			
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	
Non-cardiac chest 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	
Sudden cardiac death			
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	
Sudden death			
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	
Respiratory, thoracic and mediastinal disorders			
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	
Respiratory 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	
Product issues			
Device battery issue			
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	
Device malfunction			
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	
Injury, poisoning and procedural complications			
Tibia fracture			
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 disorders			
Acute myocardial infarction			
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	
Angina pectoris			
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 fibrillation			
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	
Nervous system disorders			
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	
Gastrointestinal disorders			
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	
Hepatobiliary disorders			
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 %

Non-serious adverse events	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	0 / 88 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Volume blood decreased			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Weight increased			
subjects affected / exposed	0 / 88 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	3 / 88 (3.41%)	0 / 85 (0.00%)	
occurrences (all)	3	0	
Alcohol poisoning			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	0 / 88 (0.00%)	2 / 85 (2.35%)	
occurrences (all)	0	2	
Drug dose omission			
subjects affected / exposed	3 / 88 (3.41%)	0 / 85 (0.00%)	
occurrences (all)	3	0	
Expired product administered			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	3 / 88 (3.41%)	1 / 85 (1.18%)	
occurrences (all)	3	1	
Fat embolism			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Incorrect drug administration 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			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Nodal rhythm			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Sinus bradycardia			
subjects affected / exposed	2 / 88 (2.27%)	0 / 85 (0.00%)	
occurrences (all)	2	0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Ventricular extrasystoles			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Ventricular fibrillation			
subjects affected / exposed	0 / 88 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Ventricular tachycardia			
subjects affected / exposed	1 / 88 (1.14%)	1 / 85 (1.18%)	
occurrences (all)	1	1	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 88 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia macrocytic			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Antiphospholipid syndrome			

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

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

subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Psoriasis			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Senile pruritus			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	0 / 88 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 88 (1.14%)	1 / 85 (1.18%)	
occurrences (all)	1	1	
Arthritis			
subjects affected / exposed	0 / 88 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	2 / 88 (2.27%)	0 / 85 (0.00%)	
occurrences (all)	2	0	
Dupuytren's contracture			
subjects affected / exposed	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	1 / 88 (1.14%)	1 / 85 (1.18%)	
occurrences (all)	1	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	1 / 88 (1.14%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Hyperuricaemia			
subjects affected / exposed	2 / 88 (2.27%)	1 / 85 (1.18%)	
occurrences (all)	2	1	
Hypokalaemia			
subjects affected / exposed	2 / 88 (2.27%)	2 / 85 (2.35%)	
occurrences (all)	2	3	
Hypomagnesaemia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Hypophosphataemia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	0 / 88 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Vitamin D deficiency			
subjects affected / exposed	0 / 88 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2012	• 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. • Exclusion criterion (subject with body weight <35 kg) was added to reflect updated prescribing information for FCM.
27 July 2012	• introduced changes to the risks/precautions section of the protocol to clarify the risk of hypersensitivity and anaphylactoid reactions
06 November 2013	• The upper limit for screening peak VO2 assessments (Inclusion criterion) was increased from 18 to 20 mL/kg/min • Exclusion Criterion (previously randomised in FER-CARS-05) was added • Exclusion Criterion (cardio resynchronisation therapy device implantation within 6 months prior to screening) was added • A 30-minute observation period after FCM administration was added • 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 VO2 assessment is performed • Peak work rate was added as an additional secondary efficacy endpoint •Addition of procedures for subjects with implanted cardiac rhythm management devices • Addition of new sites to the study (due to slow recruitment)
09 June 2014	• 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)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported