Clinical trial results:
A Randomised, Double-blind Controlled Phase 4 Study to Compare the Efficacy and Safety of Intravenous Ferric Carboxymaltose with Placebo in Patients with Chronic Heart Failure and Iron Deficiency

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2011-001695-19
Trial protocol	ES AT DE SE GB IE PT IT
Global end of trial date	13 February 2014

Results information

Result version number	v2 (current)
This version publication date	29 July 2016
First version publication date	06 August 2015
Version creation reason	• Correction of full data set Some errors were found in the original dataset which require correction

Trial information

Trial identification

Sponsor protocol code	FER-CARS-05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01453608
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vifor Pharma
Sponsor organisation address	Flughofstrasse 61, Glattbrugg, Switzerland, CH-8152
Public contact	Medical Information, Vifor (International) Inc., +41 58851 8222, medinfo@viforpharma.com
Scientific contact	Medical Information, Vifor (International) Inc., +41 58851 8222, 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	25 November 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine, relative to placebo, the effect of iron repletion therapy using IV ferric carboxymaltose (FCM) on functional capacity, as assessed by the 6-minute walk test (6MWT), at 24 weeks after initiation of therapy in subjects with chronic heart failure (CHF) and iron deficiency ID.

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) [2], 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 authorised 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	24 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	Russian Federation: 161
Country: Number of subjects enrolled	Ukraine: 50
Country: Number of subjects enrolled	Poland: 50
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Italy: 2

Worldwide total number of subjects	304
EEA total number of subjects	93

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)	85
From 65 to 84 years	212
85 years and over	7

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 589 subjects were screened across 41 centres in 9 countries in eastern and western Europe, and 39 centres successfully randomised 304 subjects. The subjects were randomised 1:1 to receive either undiluted bolus IV FCM injection or placebo (normal saline solution). Subjects were stratified by site and by Hb result.

Period 1

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

Blinding implementation details:

Because FCM is a dark brown solution which is easily distinguishable from placebo (i.e., saline solution), each site was required to have blinded and unblinded site personnel.
The Investigator, the subject, and the Sponsor were blinded. Unblinded site personnel (including at least 1 physician) were responsible for the preparation and administration of the study treatment. The unblinded personnel were not involved or did not perform any study assessments.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ferric carboxymaltose

Arm description:

Ferric carboxymaltose (FCM) given by injection at doses of 500 mg iron (10 mL) or 1,000 mg iron (20 mL). On Day 1, subjects received an initial single dose of 1,000 mg iron as FCM (for those with screening haemoglobin ≤ 14 g/dL) or 500 mg iron as FCM (for those with screening haemoglobin >14 g/dL). At Week 6, subjects received an additional dose of FCM based on their screening weight and screening haemoglobin (Hb) values. At weeks 12, 24 and 36, subjects received additional maintenance doses of 500 mg iron as FCM if applicable (i.e., serum ferritin <100 ng/mL or 100 to 300 ng/mL and transferrin saturation (TSAT) <20% (central laboratory results)).

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

Dosage and administration details:

Intravenous bolus dose of either 500 or 1,000 mg of FCM depending upon screening Hb and body weight. Potential additional doses on Week 6 depending upon screening Hb and body weight. Potential additional doses on Weeks 12, 24 and 36 depending upon body weight and whether serum ferritin <100 ng/mL or serum ferritin 100-300 ng/mL with transferrin saturation <20%.

Arm title	Placebo

Arm description:

Normal saline given by injection at volumes equal to the matching doses of 500 mg iron (10 mL) or 1,000 mg iron (20 mL). On Day 1, subjects received an initial single dose of 10 mL placebo (for those with screening Hb ≤ 14 g/dL) or 20 mL placebo (for those with screening Hb >14 g/dL). At Week 6, subjects received an additional dose of placebo based on their screening weight and screening Hb values. At weeks 12, 24 and 36, subjects received additional maintenance doses of placebo if applicable (i.e., serum ferritin <100 ng/mL or 100 to 300 ng/mL and TSAT <20% (central laboratory results)).

Arm type	Placebo

Investigational medicinal product name	Normal saline
Investigational medicinal product code	
Other name	NaCl solution
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous bolus dose of saline in a volume to match the doses of FCM depending upon screening Hb and body weight. Potential additional doses on Week 6 depending upon screening Hb and body weight. Potential additional doses on Weeks 12, 24 and 36 depending upon body weight and whether serum ferritin <100 ng/mL or serum ferritin 100-300 ng/mL with transferrin saturation <20%.

Number of subjects in period 1	Ferric carboxymaltose	Placebo
Started	152	152
Completed	123	128
Not completed	29	24
Adverse event, serious fatal	12	14
Physician decision	1	1
Consent withdrawn by subject	8	3
Adverse event, non-fatal	3	3
Not specified	3	1
Lost to follow-up	-	2
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Ferric carboxymaltose

Reporting group description:

Ferric carboxymaltose (FCM) given by injection at doses of 500 mg iron (10 mL) or 1,000 mg iron (20 mL). On Day 1, subjects received an initial single dose of 1,000 mg iron as FCM (for those with screening haemoglobin ≤ 14 g/dL) or 500 mg iron as FCM (for those with screening haemoglobin >14 g/dL). At Week 6, subjects received an additional dose of FCM based on their screening weight and screening haemoglobin (Hb) values. At weeks 12, 24 and 36, subjects received additional maintenance doses of 500 mg iron as FCM if applicable (i.e., serum ferritin <100 ng/mL or 100 to 300 ng/mL and transferrin saturation (TSAT) <20% (central laboratory results)).

Reporting group title	Placebo

Reporting group description:

Normal saline given by injection at volumes equal to the matching doses of 500 mg iron (10 mL) or 1,000 mg iron (20 mL). On Day 1, subjects received an initial single dose of 10 mL placebo (for those with screening Hb ≤ 14 g/dL) or 20 mL placebo (for those with screening Hb >14 g/dL). At Week 6, subjects received an additional dose of placebo based on their screening weight and screening Hb values. At weeks 12, 24 and 36, subjects received additional maintenance doses of placebo if applicable (i.e., serum ferritin <100 ng/mL or 100 to 300 ng/mL and TSAT <20% (central laboratory results)).

Reporting group values	Ferric carboxymaltose	Placebo	Total
Number of subjects	152	152	304
Age categorical Units: Subjects			
Adults (18-64 years)	48	37	85
From 65-84 years	101	111	212
85 years and over	3	4	7
Age continuous Units: years			
arithmetic mean	68.9	69.4	
standard deviation	± 9.47	± 9.41	-
Gender categorical Units: Subjects			
Female	68	74	142
Male	84	78	162
Race Units: Subjects			
Asian	0	1	1
Black	0	0	0
White	151	151	302
Other	1	0	1
Weight Units: Subjects			
< 70 kg	37	46	83
>= 70 kg	115	106	221
Height Units: cm			
arithmetic mean	166.68	166.5	
standard deviation	± 9.145	± 8.846	-

End points

End points reporting groups

Reporting group title	Ferric carboxymaltose

Reporting group description:

Ferric carboxymaltose (FCM) given by injection at doses of 500 mg iron (10 mL) or 1,000 mg iron (20 mL). On Day 1, subjects received an initial single dose of 1,000 mg iron as FCM (for those with screening haemoglobin ≤ 14 g/dL) or 500 mg iron as FCM (for those with screening haemoglobin >14 g/dL). At Week 6, subjects received an additional dose of FCM based on their screening weight and screening haemoglobin (Hb) values. At weeks 12, 24 and 36, subjects received additional maintenance doses of 500 mg iron as FCM if applicable (i.e., serum ferritin <100 ng/mL or 100 to 300 ng/mL and transferrin saturation (TSAT) <20% (central laboratory results)).

Reporting group title	Placebo

Reporting group description:

Normal saline given by injection at volumes equal to the matching doses of 500 mg iron (10 mL) or 1,000 mg iron (20 mL). On Day 1, subjects received an initial single dose of 10 mL placebo (for those with screening Hb ≤ 14 g/dL) or 20 mL placebo (for those with screening Hb >14 g/dL). At Week 6, subjects received an additional dose of placebo based on their screening weight and screening Hb values. At weeks 12, 24 and 36, subjects received additional maintenance doses of placebo if applicable (i.e., serum ferritin <100 ng/mL or 100 to 300 ng/mL and TSAT <20% (central laboratory results)).

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

Subject analysis set description:

The full analysis set was defined as all randomised subjects who received at least 1 dose of study drug and had 1 post-baseline assessment.

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

Subject analysis set description:

The full analysis set was defined as all randomised subjects who received at least 1 dose of study drug and had 1 post-baseline assessment.

Primary: Change from Baseline to Week 24 in 6-Minute Walk Test (6MWT)

End point title	Change from Baseline to Week 24 in 6-Minute Walk Test (6MWT)

End point description:

The 6MWT was performed in an area equipped for cardiopulmonary resuscitation and was administered by qualified and experienced personnel blinded to a subject's treatment allocation. Subjects were instructed to walk at their own pace while attempting to cover as much ground as possible in 6 minutes. Subjects were allowed to rest during the test, but were encouraged to resume walking as soon as they felt physically capable to do so. The distance walked in 6 minutes, to the nearest metre, was recorded. Baseline is the last non-missing assessment prior to the first dose of treatment. If a subject was hospitalized and unable to exercise, the worst non-null value across the study for all subjects was used. If a subject died prior to the visit, value was set to zero. If a subject was alive and not hospitalized, no imputation was done for missing values.
Positive change values indicate greater distance walked at week 24 and therefore improved functional capacity.

End point type	Primary

End point timeframe:

Day 1 (baseline), Week 24

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	130[1]	131[2]		
Units: meters				
least squares mean (standard error)	17.5 (± 8.16)	-15.7 (± 8)		

Notes:

[1] - Subjects with baseline and Week 24 values.

[2] - Subjects with baseline and Week 24 values.

Statistical analyses

Statistical analysis title	Change Baseline to Week 24 in 6MWT

Statistical analysis description:

The primary efficacy analyses of the change in 6MWT from Baseline to Week 24 were conducted using an analysis of covariance (ANCOVA), with adjustment for baseline 6MWT distance, Hb level at screening (<12 g/dL, ≥12 g/dL) and pooled country (Russia, Ukraine, Poland, and Pooled C (other European countries: Austria, Italy, Portugal, Spain, Sweden, and United Kingdom)).

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [3]
Method	ANCOVA
Parameter estimate	Difference in Least-Squares-Means (LSM)
Point estimate	33.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.51
upper limit	53.94
Variability estimate	Standard error of the mean
Dispersion value	10.52

Notes:

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

Secondary: Summary of Repeated Measures Analysis of the 6-Minute Walk Test (6MWT) Change from Baseline Over Time

End point title	Summary of Repeated Measures Analysis of the 6-Minute Walk Test (6MWT) Change from Baseline Over Time

End point description:

The change in 6MWT from baseline over time (i.e., to weeks 6, 12, 24, 36 and 52) was analysed with the imputation for death and hospitalisation assessment using an ANCOVA with repeated measures for the FAS. Baseline is the last non-missing assessment prior to the first dose of treatment. If a subject was hospitalized and unable to exercise, the worst non-null value across the study for all subjects was used. If a subject died prior to the visit, value was set to zero. If a subject was alive and not hospitalized, no imputation was done for missing values.
Positive change values indicate greater distance walked at week 24 and therefore improved functional capacity.

End point type	Secondary

End point timeframe:

Day 1 (baseline), Weeks 6, 12, 24, 36, 52

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150[4]	151[5]		
Units: meters				
least squares mean (standard error)				
Week 6 (n=143, 148)	14.1 (± 7.03)	0.5 (± 6.88)		
Week 12 (n=137, 146)	14.6 (± 7.18)	-1.3 (± 6.93)		
Week 24 (n=130, 131)	19.4 (± 7.36)	-13.5 (± 7.29)		
Week 36 (n=122, 123)	19.5 (± 7.57)	-22.3 (± 7.55)		
Week 52 (n=125, 121)	14.1 (± 7.5)	-22 (± 7.59)		

Notes:

[4] - # patients analyzed for each timepoint are reported within the category title.

[5] - # patients analyzed for each timepoint are reported within the category title.

Statistical analyses

Statistical analysis title	Repeated Measures 6MWT - Week 6

Statistical analysis description:

The change in 6MWT from baseline over time (i.e., to weeks 6, 12, 24, 36 and 52) was analysed with the imputation for death and hospitalisation assessment using an ANCOVA with repeated measures for the FAS. Treatment, visit, gender, age, pooled country, baseline score, and Hb level at screening (<12 g/dL or ≥12 g/dL) were included as covariates in the repeated measures model; a term of interaction between visit and treatment was also included. Subjects in this analysis is 291.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16 [6]
Method	ANCOVA with repeated measures
Parameter estimate	Difference of LSM
Point estimate	13.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.27
upper limit	32.53
Variability estimate	Standard error of the mean
Dispersion value	9.63

Notes:

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

Statistical analysis title	Repeated Measures 6MWT - Week 12

Statistical analysis description:

The change in 6MWT from baseline over time (i.e., to weeks 6, 12, 24, 36 and 52) was analysed with the imputation for death and hospitalisation assessment using an ANCOVA with repeated measures for the FAS. Treatment, visit, gender, age, pooled country, baseline score, and Hb level at screening (<12 g/dL or ≥12 g/dL) were included as covariates in the repeated measures model; a term of interaction between visit and treatment was also included. Subjects in this analysis is 283.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1 [7]
Method	ANCOVA with repeated measures
Parameter estimate	Difference of LSM
Point estimate	15.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.27
upper limit	35.07
Variability estimate	Standard error of the mean
Dispersion value	9.77

Notes:

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

Statistical analysis title	Repeated Measures 6MWT - Week 24

Statistical analysis description:

The change in 6MWT from baseline over time (i.e., to weeks 6, 12, 24, 36 and 52) was analysed with the imputation for death and hospitalisation assessment using an ANCOVA with repeated measures for the FAS. Treatment, visit, gender, age, pooled country, baseline score, and Hb level at screening (<12 g/dL or ≥12 g/dL) were included as covariates in the repeated measures model; a term of interaction between visit and treatment was also included. Subjects in this analysis is 261.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [8]
Method	ANCOVA with repeated measures
Parameter estimate	Difference of LSM
Point estimate	32.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.9
upper limit	52.82
Variability estimate	Standard error of the mean
Dispersion value	10.17

Notes:

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

Statistical analysis title	Repeated Measures 6MWT - Week 36

Statistical analysis description:

The change in 6MWT from baseline over time (i.e., to weeks 6, 12, 24, 36 and 52) was analysed with the imputation for death and hospitalisation assessment using an ANCOVA with repeated measures for the FAS. Treatment, visit, gender, age, pooled country, baseline score, and Hb level at screening (<12 g/dL or ≥12 g/dL) were included as covariates in the repeated measures model; a term of interaction between visit and treatment was also included. Subjects in this analysis is 245.

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

Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	ANCOVA with repeated measures
Parameter estimate	Difference of LSM
Point estimate	41.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.23
upper limit	62.43
Variability estimate	Standard error of the mean
Dispersion value	10.5

Notes:

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

Statistical analysis title	Repeated Measures 6MWT - Week 52

Statistical analysis description:

The change in 6MWT from baseline over time (i.e., to weeks 6, 12, 24, 36 and 52) was analysed with the imputation for death and hospitalisation assessment using an ANCOVA with repeated measures for the FAS. Treatment, visit, gender, age, pooled country, baseline score, and Hb level at screening (<12 g/dL or ≥12 g/dL) were included as covariates in the repeated measures model; a term of interaction between visit and treatment was also included. Subjects in this analysis is 246.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
Method	ANCOVA with repeated measures
Parameter estimate	Difference of LSM
Point estimate	36.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.53
upper limit	56.63
Variability estimate	Standard error of the mean
Dispersion value	10.47

Notes:

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

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."

End point type	Secondary

End point timeframe:

Week 6

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	144	147		
Units: subjects				
Has much improved	9	4		
Has (moderately) improved	21	19		
Has a little improved	35	37		
Is unchanged	70	73		
Is a little worse	6	10		
Is (moderately) worse	1	2		
Is much worse	1	1		
Died	1	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) - Placebo
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29 [11]
Method	Repeated measures polytomous model
Parameter estimate	Odds ratio (OR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.2

Notes:

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

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."

End point type	Secondary

End point timeframe:

Week 12

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	137	148		
Units: subjects				
Has much improved	10	5		
Has (moderately) improved	28	18		
Has a little improved	44	46		
Is unchanged	41	64		
Is a little worse	5	7		
Is (moderately) worse	3	3		
Is much worse	2	2		
Died	4	3		

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) - Placebo
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035 [12]
Method	Repeated measures polytomous model
Parameter estimate	Odds ratio (OR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.97

Notes:

[12] - 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.”

End point type	Secondary

End point timeframe:

Week 24

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131	130		
Units: subjects				
Has much improved	10	6		
Has (moderately) improved	21	13		
Has a little improved	38	34		
Is unchanged	45	54		
Is a little worse	8	12		
Is (moderately) worse	2	3		
Is much worse	0	3		
Died	7	5		

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) - Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047 [13]
Method	Repeated measures polytomous model
Parameter estimate	Odds ratio (OR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.99

Notes:

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

Secondary: Patient Global Assessment (PGA) At Week 36

End point title	Patient Global Assessment (PGA) At Week 36

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."

End point type	Secondary

End point timeframe:

Week 36

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	123	124		
Units: subjects				
Has much improved	12	6		
Has (moderately) improved	27	21		
Has a little improved	36	24		
Is unchanged	34	44		
Is a little worse	3	13		
Is (moderately) worse	2	1		
Is much worse	1	7		
Died	8	8		

Statistical analyses

Statistical analysis title	PGA - Week 36

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) - Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [14]
Method	Repeated measures polytomous model
Parameter estimate	Odds ratio (OR)
Point estimate	0.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.72

Notes:

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

Secondary: Patient Global Assessment (PGA) At Week 52

End point title	Patient Global Assessment (PGA) At Week 52

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."

End point type	Secondary

End point timeframe:

Week 52

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	127	119		
Units: subjects				
Has much improved	14	7		
Has (moderately) improved	20	12		
Has a little improved	38	21		
Is unchanged	32	51		
Is a little worse	9	12		
Is (moderately) worse	1	1		
Is much worse	1	1		
Died	12	14		

Statistical analyses

Statistical analysis title	PGA - Week 52

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) - Placebo

Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [15]
Method	Repeated measures polytomous model
Parameter estimate	Odds ratio (OR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.73

Notes:

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

Secondary: Patient Global Assessment (PGA) At Week 52 Endpoint

End point title	Patient Global Assessment (PGA) At Week 52 Endpoint

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 Week 52 Endpoint value used last-observation-carried-forward (LOCF).

End point type	Secondary

End point timeframe:

Last available PGA value, up to Week 52

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150	151		
Units: subjects				
Has much improved	15	8		
Has (moderately) improved	22	17		
Has a little improved	45	28		
Is unchanged	42	63		
Is a little worse	9	15		
Is (moderately) worse	3	1		
Is much worse	2	5		
Died	12	14		

Statistical analyses

Statistical analysis title	PGA - Week 52 Endpoint

Statistical analysis description:

Results for the Week 52 Endpoint analysis are from logistic regression including treatment, 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) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [16]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.81

Notes:

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

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

End point title	Change from Baseline Over Time In the New York Heart Association (NYHA) Scores

End point description:

Assessments of NYHA functional class were completed by a cardiologist.
- Class I Patients have cardiac disease but without the resulting limitations of physical activity.
- Class II Patients have slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or angina pain.
- Class III Patients marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea, or anginal pain.
- Class IV Patients an inability to carry on any physical activity without discomfort. Symptoms may be present even at rest. If any physical activity is undertaken, discomfort is increased.
- Class V Patient died

Subjects who were hospitalised at the time of assessment were imputed as "Class IV" and those who had died were imputed as "Class V."
Negative change from baseline values indicate improvement in functional class.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 6, 12, 24, 36, 52

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150[17]	151[18]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 6 (n=144, 148)	-0.028 (± 0.2883)	0.041 (± 0.2828)		
Week 12 (n=137, 148)	-0.015 (± 0.5284)	0.054 (± 0.383)		

Week 24 (n=132, 132)	-0.03 (± 0.6293)	0.114 (± 0.5191)		
Week 36 (n=123, 125)	-0.008 (± 0.7628)	0.224 (± 0.7169)		
Week 52 (n= 127, 121)	0.047 (± 0.8896)	0.322 (± 0.8681)		
Week 52 Endpoint (n=150, 151)	0.04 (± 0.8264)	0.285 (± 0.7948)		

Notes:

[17] - # patients analyzed for each timepoint are reported within the category title.

[18] - # patients analyzed for each timepoint are reported within the category title.

Statistical analyses

Statistical analysis title	NYHA - Week 6

Statistical analysis description:

The change in NYHA classification at each time point was analysed using repeated measures polytomous regression model including treatment, visit, gender, age, pooled country, baseline score and Hb level at screening (<12 g/dL or ≥12 g/dL) as covariates in the model; a term of interaction between visit and treatment was also included. Wald 95% CI are offered below.
Subjects in this analysis is 292.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067 [19]
Method	ANCOVA with repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.03

Notes:

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

Statistical analysis title	NYHA - Week 12

Statistical analysis description:

The change in NYHA classification at each time point was analysed using repeated measures polytomous regression model including treatment, visit, gender, age, pooled country, baseline score and Hb level at screening (<12 g/dL or ≥12 g/dL) as covariates in the model; a term of interaction between visit and treatment was also included. Wald 95% CI are offered below.
Subjects in this analysis is 285.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.093 [20]
Method	ANCOVA with repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	1.09

Notes:

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

Statistical analysis title	NYHA - Week 24

Statistical analysis description:

The change in NYHA classification at each time point was analysed using repeated measures polytomous regression model including treatment, visit, gender, age, pooled country, baseline score and Hb level at screening (<12 g/dL or ≥12 g/dL) as covariates in the model; a term of interaction between visit and treatment was also included. Wald 95% CI are offered below.
Subjects in this analysis is 264.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [21]
Method	ANCOVA with repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.72

Notes:

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

Statistical analysis title	NYHA - Week 36

Statistical analysis description:

The change in NYHA classification at each time point was analysed using repeated measures polytomous regression model including treatment, visit, gender, age, pooled country, baseline score and Hb level at screening (<12 g/dL or ≥12 g/dL) as covariates in the model; a term of interaction between visit and treatment was also included. Wald 95% CI are offered below.
Subjects in this analysis is 248.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [22]
Method	ANCOVA with repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.53

Notes:

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

Statistical analysis title	NYHA - Week 52

Statistical analysis description:

The change in NYHA classification at each time point was analysed using repeated measures polytomous regression model including treatment, visit, gender, age, pooled country, baseline score and Hb level at screening (<12 g/dL or ≥12 g/dL) as covariates in the model; a term of interaction between visit and treatment was also included. Wald 95% CI are offered below.
Subjects in this analysis is 248.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [23]
Method	ANCOVA with repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.52

Notes:

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

Secondary: Change from Baseline Over Time in the Fatigue Score

End point title	Change from Baseline Over Time in the Fatigue Score

End point description:

Prior to performing the 6MWT, and after vital signs were recorded, subjects completed the fatigue score self-assessment which was determined using a 10-point visual analogue fatigue scale (Version 1.1 dated 2 November 2011), ranging from 1 for no fatigue to 10 for very severe fatigue. The Week 52 Endpoint value used last-observation-carried-forward (LOCF).
Negative change scores indicate an improvement in severity of fatigue.

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment. "Pooled country" is defined as Poland, Russia, Ukraine considered separately all remaining countries are pooled together.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 6, 12, 24, 36, 52

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150[24]	151[25]		
Units: units on a scale				
least squares mean (standard error)				
Week 6 (n=139, 141)	-0.4 (± 0.13)	-0.2 (± 0.13)		
Week 12 (n=128, 138)	-0.8 (± 0.14)	-0.3 (± 0.13)		

Week 24 (n=121, 120)	-0.8 (± 0.14)	-0.2 (± 0.14)		
Week 36 (n=111, 111)	-1 (± 0.15)	-0.2 (± 0.15)		
Week 52 (n=110, 103)	-0.7 (± 0.15)	-0.1 (± 0.15)		
Week 52 Endpoint (n=146, 147)	-0.7 (± 0.15)	-0.2 (± 0.15)		

Notes:

[24] - # patients analyzed for each timepoint are reported within the category title.

[25] - # patients analyzed for each timepoint are reported within the category title.

Statistical analyses

Statistical analysis title	Fatigue Scale - Week 6

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 280.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4 [26]
Method	ANCOVA with repeating measures
Parameter estimate	Difference of LSM
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.18

Notes:

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

Statistical analysis title	Fatigue Scale - Week 12

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 266.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [27]
Method	ANCOVA with repeating measures
Parameter estimate	Difference of LSM
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.86
upper limit	-0.13

Variability estimate	Standard error of the mean
Dispersion value	0.19

Notes:

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

Statistical analysis title	Fatigue Scale - Week 24

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 241.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [28]
Method	ANCOVA with repeating measures
Parameter estimate	Difference of LSM
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.23
Variability estimate	Standard error of the mean
Dispersion value	0.2

Notes:

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

Statistical analysis title	Fatigue Scale - Week 36

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 222.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [29]
Method	ANCOVA with repeating measures
Parameter estimate	Difference of LSM
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.39
Variability estimate	Standard error of the mean
Dispersion value	0.21

Notes:

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

Statistical analysis title	Fatigue Scale - Week 52

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 213.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [30]
Method	ANCOVA with repeating measures
Parameter estimate	Difference of LSM
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	-0.25
Variability estimate	Standard error of the mean
Dispersion value	0.21

Notes:

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

Statistical analysis title	Fatigue Scale - Week 52 Endpoint

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 293.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008 [31]
Method	ANCOVA with repeating measures
Parameter estimate	Difference of LSM
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.19

Notes:

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

Secondary: Change from Baseline Over Time in Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Score

End point title	Change from Baseline Over Time in Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Score

End point description:

The KCCQ is a 23-item, self-administered questionnaire that quantifies physical limitation, symptoms (stability, frequency, and burden), self-efficacy, social function, and quality of life (QoL). Scores are transformed to a range of 0 to 100, in which higher scores reflect better health status. The Overall Summary Score is the mean of the scores for physical limitation, total symptom, QoL, and social limitation.
The KCCQ was translated in the local language (validated, official versions) of each of the participating countries, and were completed by the subjects before any other procedures at each visit.
The Week 52 Endpoint value used last-observation-carried-forward (LOCF).
Positive change from baseline scores indicate improving health status.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 6, 12, 24, 36, 52

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150[32]	151[33]		
Units: units on a scale				
least squares mean (standard error)				
Week 6 (n=143, 146)	4.3 (± 1.11)	2.6 (± 1.09)		
Week 12 (n=131, 143)	7.1 (± 1.16)	3.8 (± 1.1)		
Week 24 (n=125, 124)	5.5 (± 1.18)	4.1 (± 1.18)		
Week 36 (n=114, 113)	7.4 (± 1.23)	2.5 (± 1.24)		
Week 52 (n=114, 106)	6.8 (± 1.24)	2.3 (± 1.28)		
Week 52 Endpoint (n=149, 150)	5.2 (± 1.36)	0.7 (± 1.34)		

Notes:

[32] - # patients analyzed for each timepoint are reported within the category title.

[33] - # patients analyzed for each timepoint are reported within the category title.

Statistical analyses

Statistical analysis title	KCCQ Overall Summary Score - Week 6

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 289.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25 [34]
Method	ANCOVA with repeated measures
Parameter estimate	Difference in LSM
Point estimate	1.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	4.76
Variability estimate	Standard error of the mean
Dispersion value	1.52

Notes:

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

Statistical analysis title	KCCQ Overall Summary Score - Week 12

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 274.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035 [35]
Method	ANCOVA with repeated measures
Parameter estimate	Difference in LSM
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	6.39
Variability estimate	Standard error of the mean
Dispersion value	1.57

Notes:

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

Statistical analysis title	KCCQ Overall Summary Score - Week 24

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 249.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41 [36]
Method	ANCOVA with repeated measures
Parameter estimate	Difference in LSM
Point estimate	1.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.88
upper limit	4.57
Variability estimate	Standard error of the mean
Dispersion value	1.64

Notes:

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

Statistical analysis title	KCCQ Overall Summary Score - Week 36

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 227.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [37]
Method	ANCOVA with repeated measures
Parameter estimate	Difference in LSM
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.59
upper limit	8.34
Variability estimate	Standard error of the mean
Dispersion value	1.72

Notes:

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

Statistical analysis title	KCCQ Overall Summary Score - Week 52

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 220.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [38]
Method	ANCOVA with repeated measures
Parameter estimate	Difference in LSM
Point estimate	4.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	7.94
Variability estimate	Standard error of the mean
Dispersion value	1.75

Notes:

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

Statistical analysis title	KCCQ Overall Summary Score - Week 52 Endpoint

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 299.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011 [39]
Method	ANCOVA with repeated measures
Parameter estimate	Difference in LSM
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	7.93
Variability estimate	Standard error of the mean
Dispersion value	1.76

Notes:

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

Secondary: Change from Baseline Over Time in Kansas City Cardiomyopathy Questionnaire (KCCQ) Symptom Frequency Score

End point title	Change from Baseline Over Time in Kansas City Cardiomyopathy Questionnaire (KCCQ) Symptom Frequency Score

End point description:

The KCCQ is a 23-item, self-administered questionnaire that quantifies physical limitation, symptoms (stability, frequency, and burden), self-efficacy, social function, and quality of life (QoL). Scores are transformed to a range of 0 to 100, in which higher scores reflect better health status. Only the symptom frequency score is reported in this outcome.

The KCCQ was translated in the local language (validated, official versions) of each of the participating countries, and were completed by the subjects before any other procedures at each visit.
The Week 52 Endpoint value used last-observation-carried-forward (LOCF).
Positive change from baseline scores indicate improving health status.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 6, 12, 24, 36, 52

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150[40]	151[41]		
Units: units on a scale				
least squares mean (standard error)				
Week 6 (n=142, 145)	5 (± 1.49)	2.6 (± 1.46)		
Week 12 (n=131, 141)	6.6 (± 1.55)	5 (± 1.49)		
Week 24 (n=124, 123)	5.9 (± 1.59)	3.2 (± 1.58)		
Week 36 (n=114, 112)	5.6 (± 1.65)	2.1 (± 1.67)		
Week 52 (n=114, 106)	6 (± 1.65)	0.5 (± 1.71)		
Week 52 Endpoint (n=148, 149)	3.2 (± 1.82)	-1.1 (± 1.79)		

Notes:

[40] - # patients analyzed for each timepoint are reported within the category title.

[41] - # patients analyzed for each timepoint are reported within the category title.

Statistical analyses

Statistical analysis title	KCCQ Symptom Frequency Score - Week 6

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 287.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24 [42]
Method	ANCOVA with repeated measures
Parameter estimate	Difference in LSM
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	6.4
Variability estimate	Standard error of the mean
Dispersion value	2.04

Notes:

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

Statistical analysis title	KCCQ Symptom Frequency Score - Week 12

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 272.

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

Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44 [43]
Method	ANCOVA with repeated measures
Parameter estimate	Difference in LSM
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.51
upper limit	5.73
Variability estimate	Standard error of the mean
Dispersion value	2.1

Notes:

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

Statistical analysis title	KCCQ Symptom Frequency Score - Week 24

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 247.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22 [44]
Method	ANCOVA with repeated measures
Parameter estimate	Difference in LSM
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	7.04
Variability estimate	Standard error of the mean
Dispersion value	2.2

Notes:

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

Statistical analysis title	KCCQ Symptom Frequency Score - Week 36

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 226.

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

Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13 [45]
Method	ANCOVA with repeated measures
Parameter estimate	Difference in LSM
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	8.04
Variability estimate	Standard error of the mean
Dispersion value	2.3

Notes:

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

Statistical analysis title	KCCQ Symptom Frequency Score - Week 52

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 220.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019 [46]
Method	ANCOVA with repeated measures
Parameter estimate	Difference in LSM
Point estimate	5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	10.05
Variability estimate	Standard error of the mean
Dispersion value	2.34

Notes:

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

Statistical analysis title	KCCQ Symptom Frequency Score - Week 52 Endpoint

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment.
Subjects in this analysis is 297.

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

Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.066 [47]
Method	ANCOVA with repeated measures
Parameter estimate	Difference in LSM
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	8.96
Variability estimate	Standard error of the mean
Dispersion value	2.35

Notes:

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

Secondary: Change from Baseline Over Time in the European Quality of Life 5D (EQ-5D) Questionnaire Index Score

End point title	Change from Baseline Over Time in the European Quality of Life 5D (EQ-5D) Questionnaire Index Score

End point description:

The EQ-5D is a descriptive system of health-related QoL consisting of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each dimension, subjects gave 1 of 3 responses for severity (1=no problems; 2=some or moderate problems; and 3=extreme problems/not able to do). A EQ-5D index score was calculated using the algorithm from the UK scoring methodology currently advised for a European based trial. Full health receives a score of 1; scores of 2 or 3 for any of the five dimensions plus combinations of scores result in subtractions from the 'full health' index score of 1.
The Week 52 Endpoint value used last-observation-carried-forward (LOCF).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 6, 12, 24, 36, 52

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150[48]	151[49]		
Units: units on a scale				
least squares mean (standard error)				
Week 6 (n=143, 146)	0.0262 (± 0.01471)	0.0236 (± 0.01449)		
Week 12 (n=131, 141)	0.0434 (± 0.01537)	0.0522 (± 0.01475)		
Week 24 (n=125, 124)	0.0571 (± 0.01571)	0.0617 (± 0.01567)		
Week 36 (n=114, 113)	0.0553 (± 0.01637)	0.0019 (± 0.01646)		
Week 52 (n=114, 106)	0.0367 (± 0.01639)	0.0425 (± 0.01692)		
Week 52 Endpoint (n=149, 150)	0.0301 (± 0.01712)	0.0255 (± 0.01683)		

Notes:

[48] - # patients analyzed for each timepoint are reported within the category title.

[49] - # patients analyzed for each timepoint are reported within the category title.

Statistical analyses

Statistical analysis title	EQ-5D - Week 6

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment. "Pooled country" is defined as Poland, Russia, Ukraine considered separately all remaining countries are pooled together.
Subjects in this analysis is 289.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9 [50]
Method	ANCOVA with repeated measures
Parameter estimate	Difference of LSM
Point estimate	0.0026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.037
upper limit	0.0423
Variability estimate	Standard error of the mean
Dispersion value	0.02021

Notes:

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

Statistical analysis title	EQ-5D - Week 12

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment. "Pooled country" is defined as Poland, Russia, Ukraine considered separately all remaining countries are pooled together.
Subjects in this analysis is 272.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67 [51]
Method	ANCOVA with repeated measures
Parameter estimate	Difference of LSM
Point estimate	-0.0088
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0497
upper limit	0.0321

Variability estimate	Standard error of the mean
Dispersion value	0.02084

Notes:

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

Statistical analysis title	EQ-5D - Week 24

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment. "Pooled country" is defined as Poland, Russia, Ukraine considered separately all remaining countries are pooled together.
Subjects in this analysis is 249.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83 [52]
Method	ANCOVA with repeated measures
Parameter estimate	Difference of LSM
Point estimate	-0.0046
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0474
upper limit	0.0381
Variability estimate	Standard error of the mean
Dispersion value	0.02177

Notes:

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

Statistical analysis title	EQ-5D - Week 36

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment. "Pooled country" is defined as Poland, Russia, Ukraine considered separately all remaining countries are pooled together.
Subjects in this analysis is 227.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [53]
Method	ANCOVA with repeated measures
Parameter estimate	Difference of LSM
Point estimate	0.0534
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0086
upper limit	0.0981
Variability estimate	Standard error of the mean
Dispersion value	0.0228

Notes:

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

Statistical analysis title	EQ-5D - Week 52

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment. "Pooled country" is defined as Poland, Russia, Ukraine considered separately all remaining countries are pooled together.
Subjects in this analysis is 220.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8 [54]
Method	ANCOVA with repeated measures
Parameter estimate	Difference of LSM
Point estimate	-0.0058
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0513
upper limit	0.0397
Variability estimate	Standard error of the mean
Dispersion value	0.02318

Notes:

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

Statistical analysis title	EQ-5D - Week 52 Endpoint

Statistical analysis description:

Least-Squares-Means are from an ANCOVA with repeated measures model with treatment, visit, gender, age, pooled country, baseline value, haemoglobin level at screening (<12g/dL, >=12g/dL). Also interaction between visit and treatment. "Pooled country" is defined as Poland, Russia, Ukraine considered separately all remaining countries are pooled together.
Subjects in this analysis is 299.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84 [55]
Method	ANCOVA with repeated measures
Parameter estimate	Difference of LSM
Point estimate	0.0046
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0388
upper limit	0.048
Variability estimate	Standard error of the mean
Dispersion value	0.02206

Notes:

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

Secondary: Kaplan-Meier Estimates for Time to First Hospitalization

End point title	Kaplan-Meier Estimates for Time to First Hospitalization

End point description:

Time-to-event was calculated as (date of event – date of first study medication administration) + 1. Endpoint is defined as any time post baseline and on/before completion or withdrawal. Subjects are censored at completion or withdrawal.
Values of 999 indicates the time could not be calculated due to insufficient events.

End point type	Secondary

End point timeframe:

Day 1 up to day 418

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150	151		
Units: days				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Time to First Hospitalisation

Statistical analysis description:

The hazard ratio and associated 95% CI comes from the proportional hazards modeling.

Comparison groups	Full analysis set (FAS) - Placebo v Full analysis set (FAS) - FCM
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.144 [56]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.1

Notes:

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

Secondary: Kaplan-Meier Estimates for Time to Death

End point title	Kaplan-Meier Estimates for Time to Death

End point description:

Time-to-event was calculated as (date of event – date of first study medication administration) + 1. Endpoint is defined as any time post baseline and on/before completion or withdrawal. Subjects are censored at completion or withdrawal.
Values of 999 indicates the time could not be calculated due to insufficient events.

End point type	Secondary

End point timeframe:

Day 1 up to Day 418

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150	151		
Units: days				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Time to Death

Statistical analysis description:

The hazard ratio and associated 95% CI comes from the proportional hazards modeling.

Comparison groups	Full analysis set (FAS) - FCM v Full analysis set (FAS) - Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.771 [57]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.9

Notes:

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

Secondary: Subjects with Treatment-Emergent Adverse Events (TEAE)

End point title	Subjects with Treatment-Emergent Adverse Events (TEAE)

End point description:

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration, at any dose, of a medicinal or therapeutic product whether or not considered related to that product. Relation to study drug was assessed by the investigator. Severity was rated by the investigator on a scale of 1 (mild) to 3 (severe - defined as incapacitating and the subject is unable to work or complete usual activity). Serious AEs include death (death due to progressive disease were not reported as an SAE), a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or

significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized the patient and required medical intervention to prevent the previously listed serious outcomes.

End point type	Secondary

End point timeframe:

Day 1 up to Week 52

End point values	Ferric carboxymaltose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152[58]	152[59]		
Units: subjects				
Any TEAE	121	115		
Any severe TEAE	21	27		
Any serious TEAE	43	53		
TEAE leading to study drug withdrawal	14	19		
TEAE with outcome of death	13	14		
Treatment-related TEAE	14	5		
Severe treatment-related TEAE	0	0		
Serious treatment-related TEAE	0	0		
Related TEAE leading to study drug withdrawal	1	0		
Related TEAE with outcome of death	0	0		

Notes:

[58] - Safety set

[59] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: Cardiac Disorders Occurring in >2% of Subjects

End point title	Cardiac Disorders Occurring in >2% of Subjects

End point description:

"Any cardiac failure event" includes the following preferred terms: cardiac failure, cardiac failure chronic, cardiac failure acute, acute left ventricular failure, cardiogenic shock, and left ventricular failure.

End point type	Secondary

End point timeframe:

Day 1 to Week 52

End point values	Ferric carboxymaltose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152[60]	152[61]		
Units: subjects				
Any cardiac disorder	58	57		
Any cardiac failure event	21	36		

Cardiac failure chronic	9	13		
Cardiac failure	9	23		
Atrial fibrillation	9	7		
Angina pectoris	8	6		
Sinus bradycardia	6	1		
Cardiac failure acute	4	2		
Ventricular extrasystoles	1	4		

Notes:

[60] - Safety set

[61] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Hospitalisations

End point title	Percentage of Subjects with Hospitalisations

End point description:

Only treatment-emergent adverse events leading to hospitalisation were adjudicated for this analysis. Adjudication was performed by the independent and blinded Clinical Adjudication Committee. Where multiple events led to the same hospitalisation, then only the primary reason for hospitalisation was adjudicated. Incidence of hospitalisation was computed as the number of subjects who experienced adverse events leading to hospitalisation divided by the number of subjects in that treatment group.
CHF - chronic heart failure
CV - cardiovascular

End point type	Secondary

End point timeframe:

Day 1 to Week 52

End point values	Full analysis set (FAS) - FCM	Full analysis set (FAS) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150	151		
Units: percentage of subjects				
number (not applicable)				
Any (all-cause) hospitalisation	21.3	29		
Due to worsening CHF	6.7	16.6		
Due to other CV related event (not CHF)	8.7	9.9		
Due to a non-CV related event	10	9.9		
Insufficient data for adjudication	0	0.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Estimated Glomerular Filtration Rate (eGFR) Using the Formula for Modification of Diet in Renal Disease 6 (MDRD6)

End point title	Change in Estimated Glomerular Filtration Rate (eGFR) Using

	the Formula for Modification of Diet in Renal Disease 6 (MDRD6)

End point description:

The MDRD6 formula is: eGFR=161.5 * (standardised serum creatinine * 0.0113)^-0.999 * (age)^-0.176 * (BUN mmol/L * 2.801)^-0.17 * (albumin g/L * 0.1)^0.318 * 1.18 (if African American) * 0.762 (if female). Given that the reliability of the MDRD6 formula is limited for results >60 mL/min/1.73 m^2, all results for MDRD6 which were reported by the laboratory as >60 mL/min/1.73 m^2 were rounded up to 61, therefore limiting the interpretation of summary statistics for this data.
The Week 52 Endpoint value used last-observation-carried-forward (LOCF).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 6, 12, 24, 36, 52

End point values	Ferric carboxymaltose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152[62]	152[63]		
Units: mL/min/SSA				
arithmetic mean (standard deviation)				
Week 6 (n=142, 146)	-0.4 (± 5.79)	0 (± 6.66)		
Week 12 (n=128, 143)	-0.3 (± 6.75)	-0.1 (± 6.05)		
Week 24 (n=124, 123)	-0.9 (± 6.7)	-0.2 (± 5.78)		
Week 36 (n=113, 112)	-0.7 (± 6.98)	-0.6 (± 7.6)		
Week 52 (n=114, 105)	-1.5 (± 6.77)	-0.7 (± 7.47)		
Week 52 Endpoint (n=148, 150)	-1.7 (± 6.65)	-0.5 (± 6.95)		

Notes:

[62] - Safety set
patients analyzed for each timepoint are reported within the category title.
[63] - Safety set
patients analyzed for each timepoint are reported within the category title.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Estimated Glomerular Filtration Rate (eGFR) Using the Formula for Chronic Kidney Disease Epidemiology Collaboration (EPI-CKD)

End point title	Change in Estimated Glomerular Filtration Rate (eGFR) Using the Formula for Chronic Kidney Disease Epidemiology Collaboration (EPI-CKD)

End point description:

EPI-CKD uses a formula that takes into account race, gender and serum creatinine value.
The Week 52 Endpoint value used last-observation-carried-forward (LOCF).

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 6, 12, 24, 36, 52

End point values	Ferric carboxymaltose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152[64]	152[65]		
Units: mL/min/SSA				
arithmetic mean (standard deviation)				
Week 6 (n=141, 146)	-0.3 (± 12.26)	-1.6 (± 12.24)		
Week 12 (n=128, 143)	-0.3 (± 14.1)	-1 (± 11.68)		
Week 24 (n=124, 123)	-2.1 (± 13.45)	-0.8 (± 10.42)		
Week 36 (n=113, 112)	-1.5 (± 14.29)	-3.4 (± 13.32)		
Week 52 (n=114, 105)	-2.9 (± 14.85)	-3.5 (± 13.98)		
Week 52 Endpoint (n=148, 150)	-2.3 (± 14.2)	-2.6 (± 13.5)		

Notes:

[64] - Safety set
patients analyzed for each timepoint are reported within the category title.
[65] - Safety set
patients analyzed for each timepoint are reported within the category title.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 0 (post treatment) up to Week 52	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Normal saline given by injection at volumes equal to the matching doses of 500 mg iron (10 mL) or 1,000 mg iron (20 mL). On Day 1, subjects received an initial single dose of 10 mL placebo (for those with screening Hb ≤ 14 g /dL) or 20 mL placebo (for those with screening Hb >14 g/dL). At Week 6, subjects received an additional dose of placebo based on their screening weight and screening Hb values. At weeks 12, 24 and 36, subjects received additional maintenance doses of placebo if applicable (i.e., serum ferritin <100 ng/mL or 100 to 300 ng/mL and TSAT <20% (central laboratory results)).

Reporting group title	Ferric carboxymaltose

Reporting group description:

Ferric carboxymaltose (FCM) given by injection at doses of 500 mg iron (10 mL) or 1,000 mg iron (20 mL). On Day 1, subjects received an initial single dose of 1,000 mg iron as FCM (for those with screening Hb ≤ 14 g/dL) or 500 mg iron as FCM (for those with screening Hb >14 g/dL). At Week 6, subjects received an additional dose of FCM based on their screening weight and screening Hb values. At weeks 12, 24 and 36, subjects received additional maintenance doses of 500 mg iron as FCM if applicable (i.e., serum ferritin <100 ng/mL or 100 to 300 ng/mL and TSAT <20% (central laboratory results)).

Serious adverse events	Placebo	Ferric carboxymaltose	
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 152 (34.87%)	43 / 152 (28.29%)	
number of deaths (all causes)	14	13	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute promyelocytic leukaemia			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			

subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Essential thrombocythaemia			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Bladder catheter removal			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (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			
Device dislocation			
subjects affected / exposed	1 / 152 (0.66%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	3 / 152 (1.97%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Cardiac death			
subjects affected / exposed	0 / 152 (0.00%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Asthenia			
subjects affected / exposed	1 / 152 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device battery issue			
subjects affected / exposed	1 / 152 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 152 (1.32%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
International normalised ratio increased			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (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			
Hip fracture			
subjects affected / exposed	1 / 152 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	15 / 152 (9.87%)	5 / 152 (3.29%)	
occurrences causally related to treatment / all	0 / 19	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 2	
Cardiac failure chronic			
subjects affected / exposed	8 / 152 (5.26%)	4 / 152 (2.63%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiac failure acute			
subjects affected / exposed	2 / 152 (1.32%)	3 / 152 (1.97%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Atrial fibrillation			
subjects affected / exposed	1 / 152 (0.66%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	3 / 152 (1.97%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 152 (0.66%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Ventricular dyssynchrony			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			

subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	2 / 152 (1.32%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 152 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 152 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart valve incompetence			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
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	2 / 152 (1.32%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	2 / 152 (1.32%)	0 / 152 (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	2 / 152 (1.32%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	2 / 152 (1.32%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adam-Stokes syndrome			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac discomfort			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular dysfunction			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (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			
Embolic stroke			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 152 (1.32%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemorrhagic anaemia			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatic cyst			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	2 / 152 (1.32%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal angiodysplasia			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mesenteric vein thrombosis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 152 (0.66%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Gouty arthritis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	3 / 152 (1.97%)	3 / 152 (1.97%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 152 (0.66%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess soft tissue			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory infection			
subjects affected / exposed	2 / 152 (1.32%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 152 (1.32%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Ferric carboxymaltose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	101 / 152 (66.45%)	112 / 152 (73.68%)	
Investigations			
Blood pressure increased			
subjects affected / exposed	9 / 152 (5.92%)	12 / 152 (7.89%)	
occurrences (all)	17	35	

Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 152 (5.26%)	10 / 152 (6.58%)	
occurrences (all)	11	14	
Hypotension			
subjects affected / exposed	8 / 152 (5.26%)	7 / 152 (4.61%)	
occurrences (all)	8	8	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	5 / 152 (3.29%)	8 / 152 (5.26%)	
occurrences (all)	10	10	
Cardiac failure			
subjects affected / exposed	11 / 152 (7.24%)	5 / 152 (3.29%)	
occurrences (all)	14	5	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 152 (6.58%)	15 / 152 (9.87%)	
occurrences (all)	20	33	
Dizziness			
subjects affected / exposed	9 / 152 (5.92%)	11 / 152 (7.24%)	
occurrences (all)	15	15	
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 152 (5.92%)	9 / 152 (5.92%)	
occurrences (all)	9	9	
Respiratory tract infection viral			
subjects affected / exposed	10 / 152 (6.58%)	8 / 152 (5.26%)	
occurrences (all)	11	8	
Nasopharyngitis			
subjects affected / exposed	13 / 152 (8.55%)	7 / 152 (4.61%)	
occurrences (all)	16	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2012	• Stratification of subjects was clarified • Clarification of study drug dosing procedure was provided • Timing of the baseline assessment of left ventricular ejection fraction (LVEF) was clarified • The exclusion of subjects with anaemia due to reasons other than ID (e.g., haemoglobinopathy) was clarified • Additional information on subject withdrawal procedures was provided • Information on the procedures to follow in the event of severe anaemia was added • Risks/precautions were updated in accordance with the FCM investigator's brochure (IB) Version 14, dated 14 March 2012 • Details of the Reference Safety Information were added and SAE reporting procedures were clarified • Additional information on the procedures for 6MWT, prohibited and concomitant therapy, physical examination and rescreening of subjects was provided • Additional secondary endpoints were included, for consistency with other studies in this programme

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported