Clinical trial results:
A Randomised, Double-blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Patients Admitted for Acute Heart Failure (Affirm-AHF)

Summary

EudraCT number	2016-001467-36
Trial protocol	GB NL PL HR SE ES IT
Global end of trial date	21 July 2020

Results information

Result version number	v2 (current)
This version publication date	05 June 2021
First version publication date	08 May 2021
Version creation reason	• Correction of full data set Update of the Sponsor contact details.

Trial information

Trial identification

Sponsor protocol code	FER-CARS-06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02937454
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vifor (International) AG.
Sponsor organisation address	Rechenstrasse 37, St. Gallen , Switzerland, CH-9001
Public contact	FER-CARS-06 Clinical Study Team, Vifor (International) AG., +41 588 518 000, FER-CARS-06.study@viforpharma.com
Scientific contact	FER-CARS-06 Clinical Study Team, Vifor (International) AG., +41 588 518 000, FER-CARS-06.study@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	12 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 July 2020
Global end of trial reached?	Yes
Global end of trial date	21 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate, relative to placebo, the effect of intravenous (IV) ferric carboxymaltose (FCM) on repeated heart failure (HF) hospitalisations and cardiovascular (CV) death.

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 Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), Committee for Proprietary Medicinal Products Guideline (CPMP/ICH/135/95), 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) and in accordance with US FDA regulations.

A Steering Committee (SC), a Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) and a Clinical Endpoint Committee (CEC) were established for this trial. The SC was to ensure the scientific integrity of the trial in addition to overseeing the operational conduct. The DSMB/DMC was to oversee the safety of study participants and the CEC was to adjudicate all events suggestive of the study outcomes using predefined criteria detailed in the adjudication charter.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	21 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 69
Country: Number of subjects enrolled	Poland: 180
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Croatia: 82
Country: Number of subjects enrolled	Argentina: 48
Country: Number of subjects enrolled	Romania: 154
Country: Number of subjects enrolled	Singapore: 45
Country: Number of subjects enrolled	Ukraine: 46
Country: Number of subjects enrolled	Lebanon: 32

Country: Number of subjects enrolled	Brazil: 28
Country: Number of subjects enrolled	Italy: 113
Country: Number of subjects enrolled	Israel: 79
Country: Number of subjects enrolled	Georgia: 193
Worldwide total number of subjects	1110
EEA total number of subjects	627

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)	281
From 65 to 84 years	739
85 years and over	90

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who had been hospitalised for an AHF episode were screened to determine potential eligibility for the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	FCM (Ferric Carboxymaltose)

Arm description: -

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

Dosage and administration details:

Ferric carboxymaltose (FCM), administered by bolus intravenous (IV) injection at a dose of 10 ml or 20 ml of undiluted solution (containing 500 mg or 1,000 mg of iron respectively) depending on the participant's body weight and haemoglobin (Hb) level.

From a single dose given at Visit 2 (Week 0) up to 4 doses given over 24 weeks (at Visit 2 (Week 0), Visit 3 (Week 6), Visit 4 (Week 12) and Visit 5 (Week 24), depending on the participant's Hb levels measured prior to planned dosing dates.

Arm title	Placebo (Normal Saline (NaCl 0.9%))

Arm description: -

Arm type	Placebo
Investigational medicinal product name	NaCl (normal saline)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Normal saline (NaCl 0.9%), administered by bolus intravenous (IV) injection at a volume corresponding to the FCM dose determined by the participant's body weight and haemoglobin (Hb) level (i.e., 10 ml or 20 ml per administration).

From a single dose given at Visit 2 (Week 0) up to 4 doses given over 24 weeks (at Visit 2 (Week 0), Visit 3 (Week 6), Visit 4 (Week 12) and Visit 5 (Week 24)), depending on the participant's Hb levels measured prior to planned dosing dates.

Number of subjects in period 1	FCM (Ferric Carboxymaltose)	Placebo (Normal Saline (NaCl 0.9%))
Started	559	551
Completed	427	437
Not completed	132	114
Consent withdrawn by subject	25	12
Adverse event, non-fatal	-	1
Death	98	95
Other	8	5
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	FCM (Ferric Carboxymaltose)
Reporting group description: -	
Reporting group title	Placebo (Normal Saline (NaCl 0.9%))
Reporting group description: -	

Reporting group values	FCM (Ferric Carboxymaltose)	Placebo (Normal Saline (NaCl 0.9%))	Total
Number of subjects	559	551	1110
Age categorical Units: Subjects			
Adults (18-64 years)	139	142	281
From 65-84 years	369	370	739
85 years and over	51	39	90
Gender categorical Units: Subjects			
Female	244	250	494
Male	315	301	616
Ethnic group Units: Subjects			
Hispanic or Latino	51	50	101
Not Hispanic or Latino	498	489	987
Unknown or Not Reported	10	12	22

Subject analysis sets	
Subject analysis set title	FCM - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set (FAS): All randomised participants for whom administration of study treatment was started and who had at least one post-baseline visit (including calls), death or hospitalisation or who withdrew from the study after but not on the randomisation date.	
Subject analysis set title	Placebo - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set (FAS): All randomised participants for whom administration of study treatment was started and who had at least one post-baseline visit (including calls), death or hospitalisation or who withdrew from the study after but not on the randomisation date.	
Subject analysis set title	FCM - Covid-19 Sensitivity Analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
In the Covid-19 sensitivity analyses, follow-up time was truncated for 300 subjects due to the censoring, by between 1 and 162 days. Participants were censored in each country on the date when the first patient with COVID-19 was reported in the respective country.	
Subject analysis set title	Placebo - Covid-19 Sensitivity Analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
In the Covid-19 sensitivity analyses, follow-up time was truncated for 300 subjects due to the censoring, by between 1 and 162 days. Participants were censored in each country on the date when the first patient with COVID-19 was reported in the respective country.	

Reporting group values	FCM - FAS	Placebo - FAS	FCM - Covid-19 Sensitivity Analysis
Number of subjects	558	550	558
Age categorical Units: Subjects			
Adults (18-64 years)	139	142	142
From 65-84 years	369	370	370
85 years and over	51	39	39
Gender categorical Units: Subjects			
Female	244	250	244
Male	315	301	315
Ethnic group Units: Subjects			
Hispanic or Latino	51	50	51
Not Hispanic or Latino	498	489	498
Unknown or Not Reported	10	12	10

Reporting group values	Placebo - Covid-19 Sensitivity Analysis		
Number of subjects	550		
Age categorical Units: Subjects			
Adults (18-64 years)	139		
From 65-84 years	369		
85 years and over	51		
Gender categorical Units: Subjects			
Female	250		
Male	301		
Ethnic group Units: Subjects			
Hispanic or Latino	50		
Not Hispanic or Latino	489		
Unknown or Not Reported	12		

End points

End points reporting groups

Reporting group title	FCM (Ferric Carboxymaltose)
Reporting group description: -	
Reporting group title	Placebo (Normal Saline (NaCl 0.9%))
Reporting group description: -	
Subject analysis set title	FCM - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set (FAS): All randomised participants for whom administration of study treatment was started and who had at least one post-baseline visit (including calls), death or hospitalisation or who withdrew from the study after but not on the randomisation date.	
Subject analysis set title	Placebo - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set (FAS): All randomised participants for whom administration of study treatment was started and who had at least one post-baseline visit (including calls), death or hospitalisation or who withdrew from the study after but not on the randomisation date.	
Subject analysis set title	FCM - Covid-19 Sensitivity Analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
In the Covid-19 sensitivity analyses, follow-up time was truncated for 300 subjects due to the censoring, by between 1 and 162 days. Participants were censored in each country on the date when the first patient with COVID-19 was reported in the respective country.	
Subject analysis set title	Placebo - Covid-19 Sensitivity Analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
In the Covid-19 sensitivity analyses, follow-up time was truncated for 300 subjects due to the censoring, by between 1 and 162 days. Participants were censored in each country on the date when the first patient with COVID-19 was reported in the respective country.	

Primary: HF Hospitalizations and CV Death

End point title	HF Hospitalizations and CV Death
End point description:	
HF = Heart Failure, CV = Cardiovascular. The composite of recurrent HF hospitalizations and CV death up to 52 weeks after randomization. Total hospitalisations included first and recurrent events. If a participant was hospitalised for heart failure and died within 24 h from any cardiovascular event, this was counted as one event.	
End point type	Primary
End point timeframe:	
up to 52 weeks after randomization	

End point values	FCM - FAS	Placebo - FAS	FCM - Covid-19 Sensitivity Analysis	Placebo - Covid-19 Sensitivity Analysis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	558	550	558	550
Units: Number of events	293	372	274	363

Statistical analyses

Statistical analysis title	Rate Ratio (RR) - Full Analysis Set (FAS)
Comparison groups	FCM - FAS v Placebo - FAS
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.059 [1]
Method	Negative binomial model
Parameter estimate	Annualised event Rate Ratio (RR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.01

Notes:

[1] - Negative binomial model adjusted for baseline covariates: sex, age, HF aetiology, HF duration, and country.

Statistical analysis title	Rate Ratio (RR) - Covid-19 Sensitivity Analysis
Comparison groups	FCM - Covid-19 Sensitivity Analysis v Placebo - Covid-19 Sensitivity Analysis
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.024 [2]
Method	Negative binomial model
Parameter estimate	Annualised event Rate Ratio (RR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.96

Notes:

[2] - Negative binomial model adjusted for baseline covariates: sex, age, HF aetiology, HF duration, and country.

Secondary: Recurrent CV Hospitalisations and CV Death

End point title	Recurrent CV Hospitalisations and CV Death

End point description:

CV = Cardiovascular

The composite of recurrent CV hospitalisations and CV death at 52 weeks after randomisation.

Total hospitalisations included first and recurrent events. If a participant was hospitalised for a cardiovascular reason and died within 24 h of admission from any cardiovascular event, this was counted as one event.

End point type	Secondary

End point timeframe:

up to 52 weeks after randomization

End point values	FCM - FAS	Placebo - FAS	FCM - Covid-19 Sensitivity Analysis	Placebo - Covid-19 Sensitivity Analysis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	558	550	558	550
Units: Number of events	370	451	350	440

Statistical analyses

Statistical analysis title	Rate Ratio (RR) - Full Analysis Set (FAS)
Comparison groups	FCM - FAS v Placebo - FAS
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.05 [3]
Method	Negative binomial model
Parameter estimate	Annualised event Rate Ratio (RR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1

Notes:

[3] - Negative binomial model adjusted for baseline covariates: sex, age, HF aetiology, HF duration, and country.

Statistical analysis title	Rate Ratio (RR) - Covid-19 Sensitivity Analysis
Comparison groups	FCM - Covid-19 Sensitivity Analysis v Placebo - Covid-19 Sensitivity Analysis
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.024 [4]
Method	Negative binomial model
Parameter estimate	Annualised event Rate Ratio (RR)
Point estimate	0.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.97

Notes:

[4] - Negative binomial model adjusted for baseline covariates: sex, age, HF aetiology, HF duration, and country.

Secondary: HF Hospitalisations

End point title	HF Hospitalisations

End point description:

HF = Heart Failure

HF hospitalisations up to 52 weeks after randomisation analysed as recurrent event.

End point type	Secondary

End point timeframe:

up to 52 weeks after randomisation

End point values	FCM - FAS	Placebo - FAS	FCM - Covid-19 Sensitivity Analysis	Placebo - Covid-19 Sensitivity Analysis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	558	550	558	550
Units: Number of events	217	294	202	287

Statistical analyses

Statistical analysis title	Rate Ratio (RR) - Full Analysis Set (FAS)
Comparison groups	FCM - FAS v Placebo - FAS
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.013 [5]
Method	Negative binomial model
Parameter estimate	Annualised event Rate Ratio (RR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.94

Notes:

[5] - Negative binomial model adjusted for baseline covariates: sex, age, HF aetiology, HF duration, and country.

Statistical analysis title	Rate Ratio (RR) - Covid-19 Sensitivity Analysis
Comparison groups	FCM - Covid-19 Sensitivity Analysis v Placebo - Covid-19

	Sensitivity Analysis
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.005 [6]
Method	Negative binomial model
Parameter estimate	Annualised event Rate Ratio (RR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.9

Notes:

[6] - Negative binomial model adjusted for baseline covariates: sex, age, HF aetiology, HF duration, and country.

Secondary: Time to CV Death

End point title	Time to CV Death

End point description:

CV = Cardiovascular

CV mortality analysed as time to first event at 52 weeks after randomisation.

End point type	Secondary

End point timeframe:

at 52 weeks after randomisation

End point values	FCM - FAS	Placebo - FAS	FCM - Covid-19 Sensitivity Analysis	Placebo - Covid-19 Sensitivity Analysis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	558	550	558	550
Units: Participants	77	78	73	76

Statistical analyses

Statistical analysis title	Hazard Ratio (HR) - Full Analysis Set (FAS)
Comparison groups	FCM - FAS v Placebo - FAS
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.809 [7]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.32

Notes:

[7] - Cox regression adjusted for sex, age, HF aetiology, HF duration, and country at baseline.

Statistical analysis title	Hazard Ratio (HR) - Covid-19 Sensitivity Analysis
Comparison groups	FCM - Covid-19 Sensitivity Analysis v Placebo - Covid-19 Sensitivity Analysis
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.687 [8]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.29

Notes:

[8] - Cox regression adjusted for sex, age, HF aetiology, HF duration, and country at baseline

Secondary: Composite of HF Hospitalisations or CV Death

End point title	Composite of HF Hospitalisations or CV Death

End point description:

HF = Heart Failure, CV = Cardiovascular

Analysed as time to first event at 52 weeks after randomisation. The number of participants with at least one HF Hospitalisation or CV Death is presented below.

End point type	Secondary

End point timeframe:

at 52 weeks after randomisation

End point values	FCM - FAS	Placebo - FAS	FCM - Covid-19 Sensitivity Analysis	Placebo - Covid-19 Sensitivity Analysis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	558	550	558	550
Units: Participants	181	209	175	205

Statistical analyses

Statistical analysis title	Hazard Ratio (HR) - Full Analysis Set (FAS)
Comparison groups	FCM - FAS v Placebo - FAS
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.03 [9]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.98

Notes:

[9] - Cox regression adjusted for sex, age, HF aetiology, HF duration, and country at baseline

Statistical analysis title	Hazard Ratio (HR) - Covid-19 Sensitivity Analysis
Comparison groups	FCM - Covid-19 Sensitivity Analysis v Placebo - Covid-19 Sensitivity Analysis
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.023 [10]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.97

Notes:

[10] - Cox regression adjusted for sex, age, HF aetiology, HF duration, and country at baseline.

Secondary: Days Lost Due to HF Hospitalisation or CV Death

End point title	Days Lost Due to HF Hospitalisation or CV Death

End point description:

HF = Heart Failure, CV = Cardiovascular

Number of days lost due to heart failure hospitalisations or cardiovascular death corresponds to the total number of days in hospital for heart failure from randomisation to last known date. Days lost due to cardiovascular death are added to the number of days lost due to heart failure hospitalisation.

End point type	Secondary

End point timeframe:

at 52 weeks after randomisation

End point values	FCM - FAS	Placebo - FAS	FCM - Covid-19 Sensitivity Analysis	Placebo - Covid-19 Sensitivity Analysis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	558	550	558	550
Units: Days				
arithmetic mean (standard deviation)	3.8 (± 9.06)	6.2 (± 14.48)	3.5 (± 8.18)	6.1 (± 14.42)

Statistical analyses

Statistical analysis title	Rate Ratio (RR) - Full Analysis Set (FAS)
Comparison groups	FCM - FAS v Placebo - FAS
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.035 [11]
Method	Negative binomial model
Parameter estimate	Annualised event Rate Ratio (RR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.97

Notes:

[11] - Negative binomial model adjusted for baseline covariates: sex, age, HF aetiology, HF duration, and country.

Statistical analysis title	Rate Ratio (RR) - Covid-19 Sensitivity Analysis
Comparison groups	Placebo - Covid-19 Sensitivity Analysis v FCM - Covid-19 Sensitivity Analysis
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009 [12]
Method	Negative binomial model
Parameter estimate	Annualised event Rate Ratio (RR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.88

Notes:

[12] - Negative binomial model adjusted for baseline covariates: sex, age, HF aetiology, HF duration, and country.

Other pre-specified: Time to HF Hospitalisation

End point title	Time to HF Hospitalisation

End point description:

HF = Heart Failure

Number of participants with at least one HF Hospitalisation up to 52 weeks after randomisation (analysed as time to first event)

End point type	Other pre-specified

End point timeframe:

up to 52 weeks after randomisation

End point values	FCM - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	558	550		
Units: Participants	142	178		

Statistical analyses

Statistical analysis title	Hazard ratio (HR)
Comparison groups	FCM - FAS v Placebo - FAS
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006 [13]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.92

Notes:

[13] - Cox regression adjusted for sex, age, HF aetiology, HF duration, and country at baseline.

Other pre-specified: Time to first CV Hospitalisation

End point title	Time to first CV Hospitalisation

End point description:

CV = Cardiovascular

Number of participants with at least one CV Hospitalisation up to 52 weeks after randomisation (analysed as a recurrent event and time to first event)

End point type	Other pre-specified

End point timeframe:

up to 52 weeks after randomisation

End point values	FCM - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	558	550		
Units: Participants	181	220		

Statistical analyses

Statistical analysis title	Hazard ratio (HR)
Comparison groups	FCM - FAS v Placebo - FAS
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009 [14]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	0.94

Notes:

[14] - Cox regression adjusted for sex, age, HF aetiology, HF duration, and country at baseline.

Other pre-specified: All-cause Mortality Analysed as Time to First Event

End point title	All-cause Mortality Analysed as Time to First Event

End point description:

Number of participants who died analysed as time to first event up to 52 weeks after randomisation

End point type	Other pre-specified

End point timeframe:

up to 52 weeks after randomisation

End point values	FCM - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	558	550		
Units: Participants	98	96		

Statistical analyses

Statistical analysis title	Hazard ratio (HR)
Comparison groups	FCM - FAS v Placebo - FAS

Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.944 [15]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.31

Notes:

[15] - Cox regression adjusted for sex, age, HF aetiology, HF duration, and country at baseline.

Other pre-specified: Change From Baseline in NYHA Functional Class

End point title	Change From Baseline in NYHA Functional Class

End point description:

NYHA = New York Heart Association

NYHA functional class was assessed as Class I, II, III, IV or V. Class V was imputed for participants who died. If a
participant was hospitalised at any point during any post-baseline visit and did not have any NYHA assessment for this visit, then Class IV was to be imputed for the visit.

Lower response categories are better for score NYHA.

End point type	Other pre-specified

End point timeframe:

at 6, 12, 24 and 52 weeks after randomisation

End point values	FCM - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	558	550		
Units: Participants				
Baseline - Class I	14	8		
Baseline - Class II	255	240		
Baseline - Class III	272	277		
Baseline - Class IV	16	22		
Baseline - Class V	0	0		
Week 6 - Class I	38	38		
Week 6 - Class II	296	271		
Week 6 - Class III	151	151		
Week 6 - Class IV	13	31		
Week 6 - Class V	18	23		
Week 12 - Class I	39	40		
Week 12 - Class II	296	267		
Week 12 - Class III	107	131		
Week 12 - Class IV	14	18		
Week 12 - Class V	36	32		
Week 24 - Class I	47	47		

Week 24 - Class II	288	265		
Week 24 - Class III	88	100		
Week 24 - Class IV	13	20		
Week 24 - Class V	56	63		
Week 52 - Class I	48	53		
Week 52 - Class II	234	223		
Week 52 - Class III	61	75		
Week 52 - Class IV	7	17		
Week 52 - Class V	99	95		

Statistical analyses

Statistical analysis title	Odds Ratio (OR)
Comparison groups	FCM - FAS v Placebo - FAS
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.196 [16]
Method	Generalised Estimating Equations (GEE)
Parameter estimate	Odds ratio (OR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.39

Notes:

[16] - The following variables are included in the GEE model: treatment, visit, baseline NYHA class, sex, age, HF aetiology, HF duration, and country

Other pre-specified: Change From Baseline in the EQ-5D-5L Questionnaire Indexed Value

End point title	Change From Baseline in the EQ-5D-5L Questionnaire Indexed Value

End point description:

EQ-5D-5L: European Quality of Life-5 Dimensions-5 Levels

The EQ 5D questionnaire consists of a health descriptive system for participants to self-classify and rate their health status on the day of administration.

The descriptive system includes 5 items/dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, which are coded from 1 (best state) to 5 (worst state).

End point type	Other pre-specified

End point timeframe:

at 6, 24 and 52 weeks after randomisation

End point values	FCM - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	558	550		
Units: Change from baseline in EQ-5D-5L				
arithmetic mean (standard error)				
Week 6	0.05 (± 0.01)	0.03 (± 0.01)		
Week 24	0.06 (± 0.01)	0.05 (± 0.01)		
Week 52	0.06 (± 0.01)	0.06 (± 0.01)		

Statistical analyses

Statistical analysis title	Mixed-effect model of repeated measures

Statistical analysis description:

MMRM using unstructured covariance matrix: Change score = Baseline score + Treatment + Visit + Treatment*Visit + Baseline covariates.

Comparison groups	FCM - FAS v Placebo - FAS
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05 [17]
Method	Mixed-effect model of repeated measures

Notes:

[17] - Week 6 : p = 0.208
Week 24 : p = 0.408
Week 52 : p = 0.999

Other pre-specified: KCCQ-12 Repeated-Measures Model for Analysis of Treatment Difference

End point title	KCCQ-12 Repeated-Measures Model for Analysis of Treatment Difference

End point description:

KCCQ = Kansas City Cardiomyopathy Questionnaire

The KCCQ 12 is a health-related quality of life questionnaire for Heart Failure. It is a 12 item questionnaire that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge and Quality of life. Scores are generated for each domain and scaled from 0 to 100, with 0 denoting the lowest reportable health status and 100 the highest reportable health status.

End point type	Other pre-specified

End point timeframe:

up to 52 weeks after randomisation

End point values	FCM - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	558	550		
Units: KCCQ-12 score				
arithmetic mean (standard error)				
Week 2	18.53 (± 1.16)	17.24 (± 1.19)		
Week 4	21.26 (± 1.18)	18.36 (± 1.21)		
Week 6	23.49 (± 1.20)	19.88 (± 1.23)		
Week 12	25.57 (± 1.24)	21.88 (± 1.26)		
Week 24	26.30 (± 1.26)	23.32 (± 1.27)		
Week 36	25.78 (± 1.28)	23.70 (± 1.30)		
Week 52	25.75 (± 1.33)	24.31 (± 1.34)		

Statistical analyses

Statistical analysis title	Mixed-effect model of repeated measures

Statistical analysis description:

MMRM using unstructured covariance matrix: Change score = Baseline score + Treatment + Visit + Treatment*Visit + Baseline covariates.

Comparison groups	FCM - FAS v Placebo - FAS
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.227 [18]
Method	Mixed-effect model of repeated measures

Notes:

[18] - Week 2: p =0.227
Week 4: p =0.018
Week 6: p =0.005
Week 12: p =0.006
Week 24: p =0.028
Week 36: p =0.136
Week 52: p =0.329

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During treatment period up to 52 weeks after randomization.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	FCM (Ferric Carboxymaltose)
Reporting group description: -	
Reporting group title	Placebo (Normal Saline (NaCl 0.9%))
Reporting group description: -	

Serious adverse events	FCM (Ferric Carboxymaltose)	Placebo (Normal Saline (NaCl 0.9%))	
Total subjects affected by serious adverse events			
subjects affected / exposed	250 / 559 (44.72%)	282 / 551 (51.18%)	
number of deaths (all causes)	99	96	
number of deaths resulting from adverse events	99	96	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cerebral ischaemia			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Rectal cancer			
subjects affected / exposed	3 / 559 (0.54%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric cancer			

subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Plasma cell myeloma			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	3 / 559 (0.54%)	3 / 551 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral vascular disorder			
subjects affected / exposed	2 / 559 (0.36%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic vascular disorder			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertension			

subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	1 / 559 (0.18%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose ulceration			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	0 / 559 (0.00%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion incomplete			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (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			
Death			
subjects affected / exposed	8 / 559 (1.43%)	13 / 551 (2.36%)	
occurrences causally related to treatment / all	0 / 8	0 / 13	
deaths causally related to treatment / all	0 / 8	0 / 13	
Sudden cardiac death			
subjects affected / exposed	5 / 559 (0.89%)	5 / 551 (0.91%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 5	0 / 5	
Sudden death			
subjects affected / exposed	5 / 559 (0.89%)	7 / 551 (1.27%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 5	0 / 7	
Multiple organ dysfunction syndrome			
subjects affected / exposed	3 / 559 (0.54%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Chest pain			
subjects affected / exposed	2 / 559 (0.36%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 559 (0.36%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	2 / 559 (0.36%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 559 (0.18%)	4 / 551 (0.73%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Generalised oedema			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			

Heart transplant rejection			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 559 (0.72%)	6 / 551 (1.09%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary oedema			
subjects affected / exposed	4 / 559 (0.72%)	5 / 551 (0.91%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	2 / 2	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 559 (0.54%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute pulmonary oedema			
subjects affected / exposed	2 / 559 (0.36%)	3 / 551 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 559 (0.36%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			

subjects affected / exposed	1 / 559 (0.18%)	3 / 551 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cough			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea at rest			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 559 (0.18%)	8 / 551 (1.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Apnoea			

subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choking			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea exertional			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopnoea			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			

subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	2 / 559 (0.36%)	4 / 551 (0.73%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Heart rate abnormal			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio decreased			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	2 / 559 (0.36%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hip fracture			

subjects affected / exposed	2 / 559 (0.36%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Post procedural haemorrhage			
subjects affected / exposed	2 / 559 (0.36%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	2 / 559 (0.36%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			

subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal injury			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative thoracic procedure complication			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin abrasion			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			

subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
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	116 / 559 (20.75%)	127 / 551 (23.05%)	
occurrences causally related to treatment / all	0 / 163	0 / 215	
deaths causally related to treatment / all	25 / 25	24 / 24	
Cardiac failure acute			
subjects affected / exposed	21 / 559 (3.76%)	17 / 551 (3.09%)	
occurrences causally related to treatment / all	0 / 25	0 / 23	
deaths causally related to treatment / all	0 / 4	0 / 2	
Cardiac failure congestive			
subjects affected / exposed	20 / 559 (3.58%)	23 / 551 (4.17%)	
occurrences causally related to treatment / all	0 / 32	0 / 35	
deaths causally related to treatment / all	0 / 3	0 / 1	
Atrial fibrillation			
subjects affected / exposed	10 / 559 (1.79%)	4 / 551 (0.73%)	
occurrences causally related to treatment / all	0 / 11	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac arrest			
subjects affected / exposed	8 / 559 (1.43%)	11 / 551 (2.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 12	
deaths causally related to treatment / all	0 / 6	0 / 9	
Angina unstable			
subjects affected / exposed	5 / 559 (0.89%)	5 / 551 (0.91%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	5 / 559 (0.89%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular arrhythmia			

subjects affected / exposed	5 / 559 (0.89%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	4 / 559 (0.72%)	7 / 551 (1.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 2	0 / 3	
Ventricular tachycardia			
subjects affected / exposed	4 / 559 (0.72%)	3 / 551 (0.54%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	3 / 559 (0.54%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 559 (0.36%)	8 / 551 (1.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 2	
Bradyarrhythmia			
subjects affected / exposed	2 / 559 (0.36%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 559 (0.36%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 3	
Ventricular fibrillation			
subjects affected / exposed	2 / 559 (0.36%)	3 / 551 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute left ventricular failure			

subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
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	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 559 (0.18%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 559 (0.18%)	3 / 551 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiomyopathy			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Congestive cardiomyopathy			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			

subjects affected / exposed	1 / 559 (0.18%)	5 / 551 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mitral valve incompetence			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 559 (0.18%)	4 / 551 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus node dysfunction			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve disease mixed			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 559 (0.00%)	3 / 551 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			

subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac amyloidosis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiorenal syndrome			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 559 (0.00%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal arrhythmia			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus bradycardia			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular dyssynchrony			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	7 / 559 (1.25%)	3 / 551 (0.54%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 6	0 / 0	
Epilepsy			
subjects affected / exposed	3 / 559 (0.54%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 559 (0.54%)	4 / 551 (0.73%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	2 / 559 (0.36%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular insufficiency			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Headache			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 559 (0.18%)	4 / 551 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Presyncope			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombotic cerebral infarction			

subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transient ischaemic attack			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 559 (0.72%)	4 / 551 (0.73%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy mediastinal			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoacusis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Corneal decompensation			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 559 (0.36%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 559 (0.36%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal ulcer			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presbyoesophagus			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 559 (0.00%)	3 / 551 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric disorder			

subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal infarction			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal ischaemia			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Melaena			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic steatosis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			

subjects affected / exposed	0 / 559 (0.00%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	8 / 559 (1.43%)	6 / 551 (1.09%)	
occurrences causally related to treatment / all	1 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal failure			
subjects affected / exposed	5 / 559 (0.89%)	5 / 551 (0.91%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 4	0 / 1	
Chronic kidney disease			
subjects affected / exposed	2 / 559 (0.36%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 559 (0.36%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
End stage renal disease			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematuria			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic nephropathy			

subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract inflammation			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Diabetic foot			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (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			
Arthralgia			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture nonunion			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain in extremity			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcopenia			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal pain			

subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	11 / 559 (1.97%)	15 / 551 (2.72%)	
occurrences causally related to treatment / all	0 / 11	0 / 16	
deaths causally related to treatment / all	0 / 1	0 / 5	
Sepsis			
subjects affected / exposed	7 / 559 (1.25%)	9 / 551 (1.63%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 4	
Bronchitis			
subjects affected / exposed	5 / 559 (0.89%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 559 (0.72%)	3 / 551 (0.54%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 559 (0.72%)	5 / 551 (0.91%)	
occurrences causally related to treatment / all	1 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Septic shock			
subjects affected / exposed	3 / 559 (0.54%)	3 / 551 (0.54%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Bacteraemia			
subjects affected / exposed	2 / 559 (0.36%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	2 / 559 (0.36%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 559 (0.36%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 559 (0.36%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	2 / 559 (0.36%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis chronic			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected COVID-19			

subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal abscess			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbuncle			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			

subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gangrene			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	0 / 559 (0.00%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	0 / 559 (0.00%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Shewanella algae bacteraemia			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tracheobronchitis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 559 (0.00%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	3 / 559 (0.54%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 559 (0.36%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperkalaemia			
subjects affected / exposed	2 / 559 (0.36%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			

subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 559 (0.18%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 559 (0.18%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 559 (0.18%)	0 / 551 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 559 (0.18%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	0 / 559 (0.00%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Decreased appetite			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoglycaemia			

subjects affected / exposed	0 / 559 (0.00%)	2 / 551 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 559 (0.00%)	1 / 551 (0.18%)	
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: 0.05 %

Non-serious adverse events	FCM (Ferric Carboxymaltose)	Placebo (Normal Saline (NaCl 0.9%))	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 559 (9.12%)	45 / 551 (8.17%)	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	51 / 559 (9.12%)	45 / 551 (8.17%)	
occurrences (all)	57	49	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2016	This amendment added serum phosphorus level to the list of locally assessed clinical laboratory parameters that were to be documented in the eCRF.
25 April 2017	This amendment made the following changes: - It was specified that study treatment administration at Week 6 (Visit 3) was to be based on iron need determined at screening. - It was clarified how natriuretic peptide levels were to be handled for subjects treated with an ARNI prior to randomisation. - The list of "secondary endpoints" was reduced by introducing a category of "other endpoints." - Procedures for the use and handling of paper-based quality of life questionnaires were clarified. - The local amendments for the UK and the Netherlands were incorporated into a single protocol document.
16 March 2018	This amendment made the following changes: - It was specified that study treatment administration at Week 6 (Visit 3) was to be based on iron need determined at screening. - It was clarified how natriuretic peptide levels were to be handled for subjects treated with an ARNI prior to randomisation. - The list of "secondary endpoints" was reduced by introducing a category of "other endpoints." - Procedures for the use and handling of paper-based quality of life questionnaires were clarified. - The local amendments for the UK and the Netherlands were incorporated into a single protocol document.
01 April 2020	This amendment made the following changes: - Text added to clarify and make explicit that if available in the subject clinical records within the index hospitalisation, serum creatinine values will also be collected before randomisation. - Measures to minimise impact of COVID-19 pandemic were added - Specification of hierarchy of secondary endpoints was added: Hochberg's procedure will be used to control the overall Type I error for the evaluation of the secondary endpoints. - New section specifying plan for pooling of results from AFFIRM and FAIR-HF2 studies was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported