Clinical trial results:
Effect of IV iron (ferric carboxymaltose, Ferinject) on exercise tolerance, symptoms and quality of life in patients with heart failure with preserved ejection fraction (HFpEF) and iron deficiency with and without anaemia

Summary

EudraCT number	2015-005757-12
Trial protocol	DE
Global end of trial date	30 December 2022

Results information

Result version number	v1 (current)
This version publication date	27 January 2024
First version publication date	27 January 2024

Trial information

Trial identification

Sponsor protocol code	FAIR-HFpEF

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Charit´- Universitätsmedizin Berlin
Sponsor organisation address	Augustenburger Platz 1, Berlin, Germany, 13353
Public contact	Division of Cardiology and Metabolism – Heart Failure, Cachexia & Sarcopenia Prof. Dr. Stefan Anker, Charité – Universitätsmedizin Berlin Medizinische Klinik m.S. Kardiologie (DHZC) , +49 30450 553092, s.anker@cachexia.de
Scientific contact	Division of Cardiology and Metabolism – Heart Failure, Cachexia & Sarcopenia Prof. Dr. Stefan Anker, Charité – Universitätsmedizin Berlin Medizinische Klinik m.S. Kardiologie (DHZC) , +49 30450 553092, stefan.anker@dhzc-charite.de

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	01 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2022
Global end of trial reached?	Yes
Global end of trial date	30 December 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary efficacy endpoint:
The primary endpoint is the difference in exercise capacity from baseline to visit 5 as assessed by the 6-minute walking test after initiation of therapy (FCM or placebo/saline) in patients with HFpEF and ID

Protection of trial subjects:

Monitor patients for elevated iron parameters or Hb levels and proceed according to stopping rule below. Procedures are decided by the un-blinded physician.
In case of elevated levels of ferritin > 800 µg/L, or ferritin > 500 µg/L when TSAT > 50%, or Hb > 16 g/dL at any stage, iron treatment has to be discontinued and placebo/saline is to be given instead. In this case, ferritin, TSAT and Hb should be re-checked at the next visit, and these visits should coincide with planned Dosing Visits and/or Assessment Visits.
In case severe anaemia develops (i.e. Hb ≤ 9 g/dL), the patient is to discontinue treatment but remain in the study and further management of anaemia is at the investigator's discretion.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 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	Germany: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

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)	3
From 65 to 84 years	35
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 7 study sites in Germany . At 6 study centres were patients enrolled.

Pre-assignment

Screening details:

A total of number of 76 subjects entered the screening period 76 patients were screened, of whom 42 remaining subjects were randomised.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	FCM-Arm

Arm description:

Subjects received intravenous ferric carboxymaltose at week 0(1-2), 16 and 32

Arm type	Experimental
Investigational medicinal product name	Ferinject
Investigational medicinal product code	7705-08-0
Other name	Ferrum (III)-Ion, Eisencarboxymaltose
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

FCM solution (Ferinject®) for parenteral application, 50 mg/mL iron. Medication will be given as a short time infusion (IV) over 15 minutes in 100mL NaCl.
5% w/v iron containing 50 mg iron per mL, as sterile solution of Ferinject® in water for injection.
Ferinject had administered in doses of 500-1000 mg at each visit via infusion

Arm title	Placebo

Arm description:

Placebo/saline patients receive the number of normal saline infusions over 15 minutes corresponding to the Ferinject® group.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Subjects received placebo (identical with study drug apart from active ingredient)

Number of subjects in period 1	FCM-Arm	Placebo
Started	20	22
Completed	16	15
Not completed	4	7
late Screen failure Patient takes immunsuppressiva	-	1
Consent withdrawn by subject	1	2
unknown	1	-
unblinded	-	1
Lost to follow-up	1	-
Protocol deviation	1	3

Baseline characteristics

Reporting groups	
Reporting group title	FCM-Arm
Reporting group description:	
Subjects received intravenous ferric carboxymaltose at week 0(1-2), 16 and 32	
Reporting group title	Placebo
Reporting group description:	
Placebo/saline patients receive the number of normal saline infusions over 15 minutes corresponding to the Ferinject® group.	

Reporting group values	FCM-Arm	Placebo	Total
Number of subjects	20	22	42
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	1	3
From 65-84 years	17	18	35
85 years and over	1	3	4
Age continuous			
Units: years			
median	78	80	
full range (min-max)	54 to 86	59 to 86	-
Gender categorical			
Units: Subjects			
Female	11	16	27
Male	9	6	15

End points

End points reporting groups

Reporting group title	FCM-Arm
Reporting group description:	
Subjects received intravenous ferric carboxymaltose at week 0(1-2), 16 and 32	
Reporting group title	Placebo
Reporting group description:	
Placebo/saline patients receive the number of normal saline infusions over 15 minutes corresponding to the Ferinject® group.	

Primary: difference in 6-minute-walking distance

End point title	difference in 6-minute-walking distance[1]
End point description:	
The primary endpoint for efficacy is the difference in 6-minute-walking distance (in meters) from baseline to visit 5. Treatment groups will be compared using a fixed effects ANCOVA model for repeated measures (MMRM): The observed change from baseline 6-minute-walking distance to each visit (visits 3 to 7) is the dependent variable. The model will include treatment, visit, treatment-visit interaction, geographic region, presence of AF at baseline, and haemoglobin status at baseline (Hb < 12g/dL vs. Hb ≥12.0 g/dL) as categorical fixed effects and age at baseline, LVEF at baseline, and baseline distance of the 6 minute-walk as continuous fixed effects. An unstructured covariance pattern will be used to estimate the variance-covariance of the within-subject repeated measures. Parameters will be estimated using REML with the Newton-Raphon algorithm and using Kenward-Roger method for calculating denominator degrees of freedom.	
End point type	Primary
End point timeframe:	
from baseline to visit 5	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was prematurely terminated due to Sponsor decision. Primary and secondary objectives were not achieved in this study due to the premature termination.

End point values	FCM-Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: meter	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: overall trial	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups	
Reporting group title	FCM-Arm
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	FCM-Arm	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 20 (15.00%)	19 / 22 (86.36%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (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			
Fracture			
subjects affected / exposed	0 / 20 (0.00%)	2 / 22 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	0 / 20 (0.00%)	3 / 22 (13.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			

subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial stenosis A subclavia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
thromboembolic event (suspected embolism)			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Heart failure (cardiac compression)			
subjects affected / exposed	0 / 20 (0.00%)	3 / 22 (13.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction (NSTEMI)			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
sensomotoric axonal polyneuropathy	Additional description: clarification of Polyneuropathy in multifunctional gait disorder (sensomotoric axonal polyneuropathy)		
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve replacement	Additional description: Aortic valve replacement (High grade aortic valve stenosis)		
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tooth extraction			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (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			
Seizure			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
stroke			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
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			
Anemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Sleep apnoea syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
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	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
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: 3 %

Non-serious adverse events	FCM-Arm	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 20 (75.00%)	17 / 22 (77.27%)	
Investigations			
cholesterol high			
subjects affected / exposed	7 / 20 (35.00%)	2 / 22 (9.09%)	
occurrences (all)	4	1	
Creatinine renal clearance increased			
subjects affected / exposed	3 / 20 (15.00%)	2 / 22 (9.09%)	
occurrences (all)	3	2	
eGFR increased			
subjects affected / exposed	2 / 20 (10.00%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
MCH increased			
subjects affected / exposed	3 / 20 (15.00%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
Cardiac disorders			
chest-pain (cardiac)			
subjects affected / exposed	1 / 20 (5.00%)	4 / 22 (18.18%)	
occurrences (all)	1	3	
Heart Failure			
subjects affected / exposed	2 / 20 (10.00%)	3 / 22 (13.64%)	
occurrences (all)	2	3	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	2 / 20 (10.00%)	2 / 22 (9.09%)	
occurrences (all)	2	2	
General disorders and administration site conditions			
edema limb			
subjects affected / exposed	3 / 20 (15.00%)	6 / 22 (27.27%)	
occurrences (all)	2	3	
Fatigue			
subjects affected / exposed	4 / 20 (20.00%)	1 / 22 (4.55%)	
occurrences (all)	4	1	

flu-like symptoms			
subjects affected / exposed	2 / 20 (10.00%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 20 (10.00%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Infections and infestations			
pneumonia/ brochchial infection			
subjects affected / exposed	0 / 20 (0.00%)	4 / 22 (18.18%)	
occurrences (all)	0	3	
Upper respiratory tract infection			
subjects affected / exposed	2 / 20 (10.00%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
Urinary tract infection			
subjects affected / exposed	1 / 20 (5.00%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 22 (9.09%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2019	new protocol version 3.5 dated, 04.06.2019: prolongation of the duration of the trial: estimated date of termination of recruitment: 30.04.2020, estimated date last patient, last visit: 30.04.2021.
25 October 2021	new protocol version 3.6, dated 01.11.2021: Prolongation of the duration of the trial: Estimated date of termination of recruitment: 30.12.2021,Estimated date last patient, last visit: 30.12.2022; Change of principal investigator in trial site
07 July 2022	new protocol version 3.7, dated 24.03.2022: Add exclusion criteria: 4. SARS-CoV-2 infection

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Trial did not collect enough data to report on the primary endpoint of the study.

Notes: