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)

Clinical Protocol Number:	FER-CARS-06
Date:	1 April 2020
Version/Amendment Number:	Version 3.1
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EudraCT Number:	2016-001467-36
Co-ordinating Investigator:	[redacted] Department of Heart Disease Medical University Cardiology Department Centre for Heart Disease Clinical Military Hospital Weigla 5, 50-891 Wroclaw Poland
Sponsor Contact:	[redacted]
Sponsor Address:	Vifor (International) Inc. Rechenstrasse 37 St. Gallen CH-9001 Switzerland

SIGNATURE PAGE

Declaration of Sponsor

Title: 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)

Version/Amendment Number/Date: Version 3.1, 1 April 2020.

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the International Council for Harmonisation Guidelines on Good Clinical Practice.

[redacted] Date (day month year)

Clinical Representative
Vifor Pharma

[redacted] Date (day month year)

Sponsor Statistician
Vifor Pharma

[redacted] Date (day month year)

Regulatory Representative
Vifor Pharma

[redacted] Date (day month year)

Sponsor Medical Expert
Vifor Pharma

SIGNATURE PAGE

Declaration of Co-ordinating Investigator

Title: 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)

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Signature of Co-ordinating Investigator	Date (day month year)

Name, Title, Address and Telephone
Number of Co-ordinating Investigator

SIGNATURE PAGE

Declaration of National Co-ordinating Investigator

Title: 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)

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Signature of National Co-ordinating Investigator	Date (day month year)

Name, Title, Address and Telephone Number of National Co-ordinating Investigator

INVESTIGATOR AGREEMENT AND SIGNATURE PAGE

I have read the attached protocol entitled 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), Version 3.1, 1 April 2020, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guidelines on Good Clinical Practice and applicable regulations and guidelines.

I agree to ensure that financial disclosure statements will be completed by:

- me (including, if applicable, my spouse (or legal partner) and dependent children)
- my Sub-Investigators

before the start of the study and to report any changes that affect my financial disclosure status for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Vifor Pharma.

Signature by the Investigator on this Protocol Signature Page documents review, agreement and approval of the requirements contained within this protocol.

Signature of Principal Investigator	Date (day month year)

Name, Title, Address and Telephone Number of Principal Investigator

SYNOPSIS

Protocol Number FER-CARS-06

Title:	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)
Short Title:	**A**ssessment o**F** **F**erric carboxymaltose to **I**mprove mo**R**bidity and **M**ortality in iron-deficient patients hospitalised for **A**cute **H**eart **F**ailure (**AFFIRM-AHF**)
Study Product(s):	Ferric carboxymaltose (FCM) or placebo
Indication:	Acute heart failure with iron deficiency (ID)
Phase:	Phase 4, therapeutic use
Sponsor:	Vifor Pharma
Study Code:	FER-CARS-06
Co-ordinating Investigator:	Prof Piotr Ponikowski, MD
Objectives:	<u>Primary Objective(s)</u> • To evaluate, relative to placebo, the effect of intravenous (IV) FCM on repeated heart failure (HF) hospitalisations and cardiovascular (CV) death. <u>Secondary Objective(s)</u> • To evaluate, relative to placebo, the effect of IV FCM on: • HF hospitalisations, CV hospitalisations, CV mortality and all-cause mortality. • Quality of life and New York Heart Association Classification (NYHA). • Tolerability and safety.
Design:	Multicentre, randomised, double-blind prospective, parallel-group, placebo-controlled, trial with a fixed follow-up of 52 weeks per subject after randomisation.
Treatment:	• Active treatment arm: IV FCM • Control treatment arm: IV NaCl 0.9% Eligible subjects will be randomised (1:1) to either FCM or placebo using a validated centralised procedure (Interactive Web-based Randomisation System (IWRS)). FCM will be supplied in 10 mL vials – one 10 mL vial contains 500 mg iron. Study treatment will be administered as an undiluted bolus injection. The study treatment dose (mL) to be administered will be determined by the subject's body weight and haemoglobin (Hb) value based on the dosing scheme per below – see Table 1

Treatment (Cont'd):

Table 1 Study Treatment Dosing Regimen

Treatment Visit	Total mL FCM or Saline				
	Weight <70 kg		Weight ≥70 kg		Any Weight
	8 g/dL[1] ≤ Hb <10 g/dL	10 g/dL ≤ Hb ≤14 g/dL	8 g/dL[1] ≤ Hb <10 g/dL	10 g/dL ≤ Hb ≤14 g/dL	14 g/dL < Hb ≤15 g/dL
Visit 2 (Week 0)	2x10 mL				1x10 mL
Visit 3[2] (Week 6)	1x10 mL	No dose	2x10 mL	1x10 mL	No dose
Visit 4, Visit 5 (Week 12, Week 24)	1x10 mL (only if ID persists)				

1 Following section in italics is applicable for The Netherlands, Spain and Singapore only (**NL, ES and SG only**) *The lower threshold of Hb values for subject eligibility prior to enrolment into the study is set to 10 g/dL. Subjects enrolled in the study in NL, ES and SG only with Hb levels that are falling below the threshold of 10 g/dL during the study will need to be withdrawn from further study treatment dosing.*

2 Dosing at Week 6 (Visit 3) will be based on the iron need upon screening Hb and weight values and only be done in subjects for whom Hb at Week 6 (Visit 3) ≤15 g/dL.

Notes: FCM=Ferric carboxymaltose; Hb=Haemoglobin; ID=Iron deficiency.

The study treatment doses administered at Visits 2 and 3 are considered as the "repletion phase" and any subsequent administrations (if ID persists) will be considered as the "maintenance phase". The first dose of study treatment will be administered for all randomised subjects at Visit 2 while the subject is still hospitalised for the Index hospitalisation. It is recommended that the first dose of study treatment is administered on the same day as randomisation. To accommodate local hospital practice, the first dose of study treatment may be administered either on the same day or the day before the planned discharge day. Note that a planned overnight stay following study treatment administration does NOT fulfil the criteria of a serious adverse event (SAE) unless there is a medical reason for doing this. The subsequent administrations of study treatment will be done as part of the outpatient clinic visits at Week 6 (Visit 3), and at Weeks 12 (Visit 4) and 24 (Visit 5). Dosing at Week 6 (Visit 3) will be based on the iron need upon screening Hb and weight values to replete iron as described in Table 1 and only be done in subjects for whom Hb at Week 6 (Visit 3) ≤15 g/dL. Maintenance dosing at Weeks 12 (Visit 4) and 24 (Visit 5) is only for subjects in whom ID persists and for whom Hb ≥8 g/dL* and ≤15 g/dL at those visits. ID is defined as serum ferritin <100 ng/mL, or 100 ng/mL ≤ serum ferritin ≤299 ng/mL if transferrin saturation (TSAT) <20%. The serum pregnancy test must also be negative for the respective visit for females of childbearing potential. Subjects will be requested to return to the outpatient clinic for the administration of study treatment maximally 7 days after the date when the blood sample was drawn.

Study treatment will be prepared by an unblinded study personnel using black syringes and once prepared, study treatment should be administered immediately thereafter using a curtain (or similar) to maintain subject blinding. Each subject should be observed for adverse effects for at least 30 minutes following each injection of study treatment. The unblinded study personnel may be involved in performing screening activities. Following randomisation the unblinded study personnel will not be operationally involved in the study for the subject concerned other than the preparation and administration of study treatment and assessment and interpretation of post-randomisation laboratory test results.

***** Following section in italics is applicable for The Netherlands, Spain and Singapore

	only (**NL, ES and SG only**): *The lower threshold of Hb values is set to 10 g/dL.*
Inclusion Criteria:	1. Currently hospitalised for an episode of acute heart failure (AHF) where AHF was the primary reason for hospitalisation. All of the following (i.e., items a to d) must apply: a. Upon admission for the AHF episode, persistent dyspnoea at rest in a recumbent sitting position (30-45°) or with minimal exertion b. Upon or during the AHF admission, at least 2 of the following clinical findings were present: i. Congestion on chest X-ray ii. Rales on chest auscultation iii. Oedema ≥1+ on a 0-3+ scale, indicating indentation of skin with mild digital pressure that requires 10 or more seconds to resolve in any dependent area including extremities or sacral region iv. Elevated jugular venous pressure (≥8 cm H_2O) c. Natriuretic peptide levels, measured ≤72 hours of the AHF admission must have been: i. Brain natriuretic peptide (BNP) ≥400 pg/mL or N-terminal-pro-brain natriuretic peptide (NT-proBNP) ≥1,600 pg/mL or ii. BNP ≥600 pg/mL or NT-proBNP ≥2,400 pg/mL for subjects presenting with atrial fibrillation when the blood sample was taken iii. For subjects treated with an angiotensin receptor neprilysin inhibitor (ARNI) in the previous 4 weeks prior to randomisation only NT-proBNP values should be considered d. AHF episode treated with minimally 40 mg of IV furosemide (or equivalent IV loop diuretic defined as 20 mg of torasemide or 1 mg of bumetanide) 2. Subject is iron deficient defined as serum ferritin <100 ng/mL or 100 ng/mL ≤ serum ferritin ≤299 ng/mL if TSAT <20%. 3. Left ventricular ejection fraction <50% (assessed and documented within 12 months prior to randomisation). 4. Male or female aged ≥18 years old. 5. Subject (or legally acceptable representative)* has provided the appropriate written informed consent. Subject must provide written informed consent before any study-specific procedures are performed. * Following section in italics is applicable for The Netherlands only (**NL only**): *The option that legally accepted representatives of subjects can sign the written informed consent is not valid for sites in The Netherlands.*

Exclusion Criteria	1. Dyspnoea due to non-cardiac causes such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, acute bronchitis, pneumonia, primary pulmonary hypertension). 2. Temperature >38°C (oral or equivalent), active infective endocarditis, sepsis, systemic inflammatory response syndrome, or any other active infection requiring anti-microbial treatment at any time during an Index hospitalisation. (Note that it does NOT include short-term prophylactic administration of antibiotics or short-term temperature elevation at admission which is no longer present at the time point of discharge/randomisation). 3. Documented restricted amyloid myocardiopathy, or acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy. (Note that it does NOT include restrictive mitral filling patterns seen on Doppler echocardiographic assessments of diastolic function). 4. Clinical evidence of acute coronary syndrome, transient ischemic attack or stroke, within the last 30 days prior randomisation. 5. Severe valvular or left ventricular outflow obstruction disease needing intervention. 6. Coronary-artery bypass graft, cardiac resynchronisation therapy device implantation, percutaneous intervention (e.g., cardiac, cerebrovascular, aortic, diagnostic catheters are allowed) or major surgery that led to significant blood loss, including thoracic and cardiac surgery, within the last 3 months prior to randomisation. 7. Subject has a body weight <35 kg at randomisation. 8. Subject at an immediate need of transfusion or with a Hb <8 g/dL* or with a Hb >15 g/dL. 9. Subjects on treatment for Vitamin B_{12} and/or serum folate deficiency. Note: Use of Vitamin B_{12} and folic acid as supplement therapy (not for deficiency treatment) is permitted. 10. Subject with a known anaemia not attributed to ID (e.g., other microcytic anaemia) or with an evidence of iron overload (e.g., haemochromatosis) or disturbances in the utilisation of iron. 11. Subject has known hypersensitivity to any of the study products to be administered or known serious hypersensitivity to other parenteral iron products. 12. Subject with known severe allergies including drug allergies, history of severe asthma, eczema or other atopic allergy and in subjects with immune or inflammatory conditions (e.g., systemic lupus erythematosus, rheumatoid arthritis). 13. History of erythropoietin stimulating agent, IV iron therapy, and/or blood transfusion in previous 3 months prior to randomisation. 14. Oral iron therapy at doses >100 mg/day in previous 4 weeks prior to randomisation. Note: Ongoing use of multivitamins containing iron <75 mg/day are permitted. 15. Currently receiving systemic chemotherapy and/or radiotherapy. 16. Renal dialysis (previous, current or planned within the next 6 months). 17. Subject has known active malignancy of any organ system, i.e., clinical evidence

	of current malignancy or not in stable remission for at least 3 years since completion of last treatment with exception of non-invasive basal cell carcinoma, squamous cell carcinoma of the skin or cervical intra-epithelial neoplasia. 18. Terminal illness other than HF with expected survival <12 months. 19. Chronic liver disease (including active hepatitis) and/or alanine transaminase or aspartate transaminase above 3 times the upper limit of the normal range. 20. Subjects with known hepatitis B surface antigen positivity and/or hepatitis C virus ribonucleic acid positivity. 21. Subject previously randomised into this study. Note: Subjects may be rescreened but when rescreened, all tests must fall inside the maximum specified screening windows for each criterion. 22. Subject is currently enrolled in or has completed any other investigational device or drug study <30 days prior to screening, or is receiving other investigational agent(s). 23. Subject is pregnant (e.g., positive human chorionic gonadotropin test) or breast feeding. 24. If of childbearing potential, subject is not using adequate contraceptive precautions. Subject must agree to use adequate contraception during the study and for 1 month after the last dose of study treatment. A highly effective method of birth control must be used. 25. Subject has a history of drug or alcohol abuse within 2 years prior to screening. 26. Subject has a significant medical condition(s), anticipated need for major surgery during the study, or any other kind of disorder that may be associated with increased risk to the subject, or may interfere with study assessments, outcomes, or the ability to provide written informed consent or comply with study procedures, in the Investigator's opinion. * Following section in italics is applicable for The Netherlands, Spain and Singapore only (**NL, ES and SG only**): *The lower threshold of Hb values is set to 10 g/dL.*
Primary and Secondary Endpoints:	<u>Primary Endpoint</u> • The composite of recurrent HF hospitalisations and CV death up to 52 weeks after randomisation. <u>Secondary Endpoints</u> The secondary endpoints will evaluate, relative to placebo, the effect of IV FCM. Hochberg's procedure will be used to control the overall Type I error for the evaluation of the secondary endpoints. The secondary endpoints are the following: • The composite of recurrent CV hospitalisations and CV death up to 52 weeks after randomisation. • HF hospitalisations up to 52 weeks after randomisation (analysed as recurrent event). • CV mortality analysed as time to first event at 52 weeks after randomisation.

- The composite of HF hospitalisations or CV death analysed as time to first event at 52 weeks after randomisation.
- Days lost due to HF hospitalisations or CV death at 52 weeks after randomisation.

Complete details concerning the analyses and statistical tests to be performed will be detailed in the SAP – the latter will be finalised prior to unblinding of the trial database.

Other Endpoints

The other endpoints will evaluate, relative to placebo, the effect of IV FCM on:

- The composite of recurrent HF hospitalisations and CV death up to 30 days after randomisation.
- The composite of recurrent CV hospitalisations and CV death up to 30 days after randomisation.
- The composite of HF hospitalisations or CV death analysed as time to first event at 30 days after randomisation.
- The composite of CV hospitalisations or CV death analysed as time to first event at 30 days after randomisation.
- HF hospitalisations up to 30 days after randomisation (analysed as recurrent event).
- HF hospitalisations up to 30 days and 52 weeks after randomisation (analysed as time to first event).
- CV hospitalisations up to 30 days and 52 weeks after randomisation (analysed as recurrent event and time to first event).
- The composite of CV hospitalisations or CV death analysed as time to first event at 30 days and 52 weeks after randomisation.
- CV mortality analysed as time to first event at 30 days after randomisation.
- All-cause mortality analysed as time to first event at 30 days and 52 weeks after randomisation.
- Proportion of patients with an event (HF hospitalisations, CV hospitalisations, CV mortality; composite and individual categories).
- Change from baseline in NYHA functional class as assessed at 6, 12, 24 and 52 weeks after randomisation.
- Change from baseline in the Kansas City Cardiomyopathy Questionnaire-12 up to 52 weeks after randomisation.
- Change from baseline in the European quality of life – 5 dimensions questionnaire up to 52 weeks after randomisation.
- Days lost due to HF hospitalisations or CV death at 30 days after randomisation.

Safety Endpoints:

- Summary of adverse events (AEs): by system organ class and preferred term (Medical Dictionary for Regulatory Activities (MedDRA) coded term), by severity and relation to study product.

	• Summary of SAEs by study treatment group presented by system organ class and preferred terms (MedDRA coded term). • Summary of clinical laboratory panels and cardiac biomarkers (absolute and change from baseline).
Procedures:	See Table 2 for full details of protocol required procedures and applicable visits (and timings). <u>Screening Visit</u> The AHF hospitalisation will be considered as the Index hospitalisation. Screening visit – performed in-hospital: • Subjects who have been hospitalised for an AHF episode will be screened to determine potential eligibility to participate in the AFFIRM-AHF trial. • The Investigator will obtain written informed consent from potentially eligible subjects before any trial-related procedure is performed. • As of the date of informed consent for each subject, the sites will document in the electronic case report form all AEs and changes/additions made to concomitant medications. SAEs will be reported as they occur but no later than 24 hours after the Investigator's awareness of the event. • A blood test will be drawn, which will be analysed locally, to determine if the subject is iron deficient and for whom Hb ≥8 g/dL* and ≤15 g/dL. The assays to be performed are: serum ferritin, TSAT and Hb. In addition, serum phosphorus levels analysed locally from the same blood draw will be documented in the eCRF. • During the same blood draw, a serum pregnancy test will be taken for females of childbearing potential. <u>Baseline Visit, Randomisation and Administration of the First Dose of Study Treatment</u> • The baseline visit will be performed in hospital (for the Index hospitalisation) upon receipt of the screening visit blood test results. • Upon receipt and review of the screening visit blood test results, the baseline visit will be performed for subjects in whom ID is confirmed and for whom the baseline Hb ≥8 g/dL* and ≤15 g/dL. In addition, for females of childbearing potential, the serum pregnancy test must be negative. The Investigator will perform/complete the baseline procedures/assessments as shown in Table 2. • In a subset of subjects samples for determination of blood biomarkers will be retained. • Upon completion of the baseline visit procedures/assessments and after the IV drugs prescribed to treat the AHF episode have been stopped for ≥12 hours, eligible subjects will be randomised using a validated centralised procedure (IWRS) to either FCM or placebo. The first dose of study treatment must be administered on the same day as randomisation. To accommodate local hospital practice, the first dose of study treatment may be administered either on the same day or the day before the planned discharge day. Note that a planned overnight stay following study treatment administration does NOT fulfil the criteria of an SAE unless there is a medical reason for doing this.

- Study treatment will be prepared and administered by unblinded study personnel who will otherwise not be involved in any study assessments for the subject concerned other than assessment and interpretation of post-randomisation laboratory test results.
- The dose of study treatment to be administered will be determined following the instructions in Table 1.

Each subject should be observed for adverse effects for at least 30 minutes following each injection of study treatment. Thereafter, the subject may be discharged from hospital, at the discretion of the Investigator.

Post-randomisation Visit

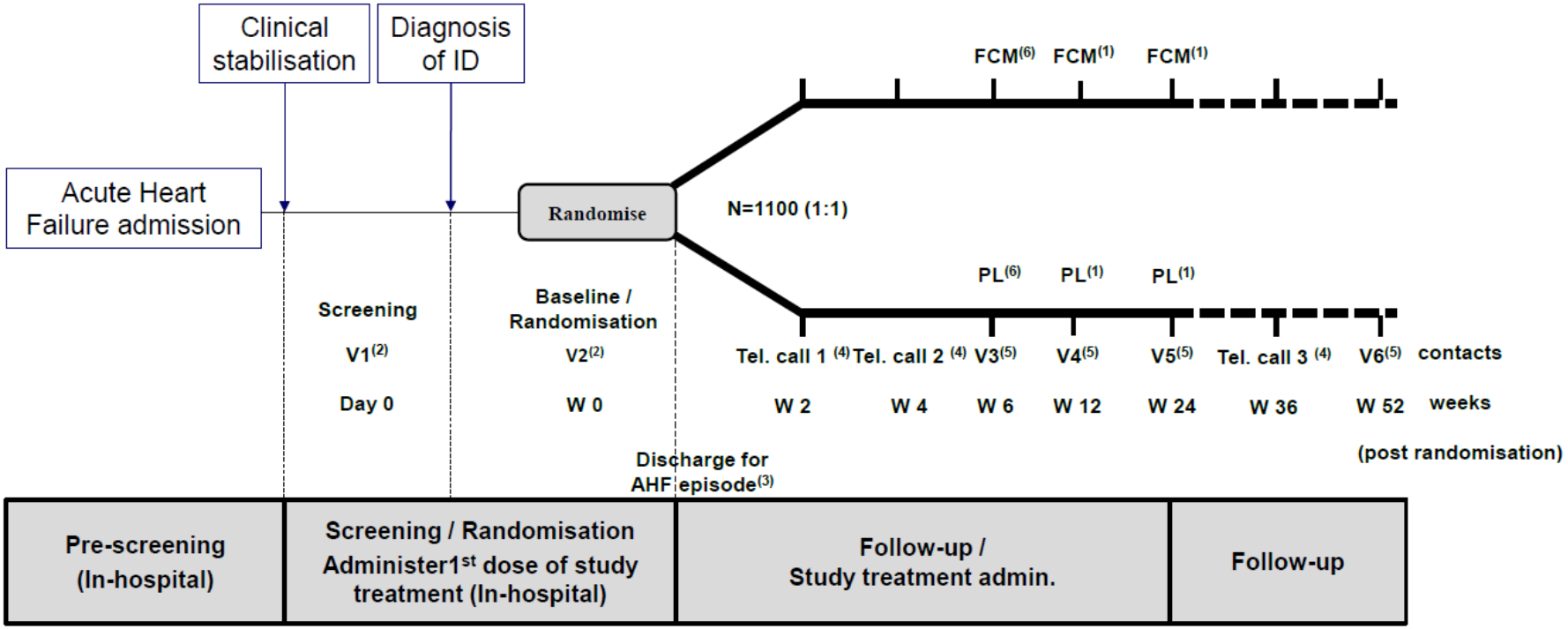
- Subjects will return to the outpatient clinic at 6, 12, 24 and 52 weeks after randomisation.

Note: due to the COVID-19 pandemic situation the Investigator can perform the 52 week visit (Visit 6) via remote methods (such as phone calls, video calls, etc.) to ensure collecting at a minimum subject's health status, AEs and concomitant medications.

- During the outpatient visits, the Investigator will perform the procedures/assessments as shown in Table 2 for the respective visit.
- At Weeks 6 (Visit 3), 12 (Visit 4), 24 (Visit 5) and 52 (Visit 6) a blood test which will be analysed locally will be performed. The assays to be performed are: serum ferritin, TSAT and Hb. In addition, serum phosphorus levels analysed locally from the same blood draw will be documented in the eCRF.
- During the same blood draw (except at Week 52 (Visit 6)), a serum pregnancy test will be taken for females of childbearing potential.
- Blood test for biomarkers at Week 6 (Visit 3), Week 24 (Visit 5) and Week 52 (Visit 6) in a subset of subjects.
- At Week 6 (Visit 3) the repletion dose of study treatment will be administered based on the iron need as assessed at the baseline visit (Table 1). Dosing will only be done in subjects for whom Hb at Week 6 (Visit 3) ≤15 g/dL and for whom the serum pregnancy test is negative in females of childbearing potential.
- If ID persists and Hb ≥8 g/dL* and ≤15 g/dL at Week 12 (Visit 4) and Week 24 (Visit 5) and for whom the serum pregnancy test is negative in females of childbearing potential, the dose of study treatment to be administered will be determined as shown in Table 1.
- Subjects for whom an administration of study treatment is necessary during an outpatient clinic visit will be requested to return to the outpatient clinic for the administration of study treatment maximally 7 days after the date when the blood sample was performed.
- Study treatment will be prepared and administered by unblinded study personnel as described in the 'Treatment' section.
- If ID persists at Week 52 (Visit 6), the Investigator will treat the ID according to local routine/standard practice.
- Subjects will be contacted by telephone at Weeks 2, 4 and 36 after randomisation – see Table 2.

	* Following section in italics is applicable for The Netherlands, Spain and Singapore only (**NL, ES and SG only**): *The lower threshold of Hb values is set to 10 g/dL.* Study Committees and Trial Oversight A Steering Committee (SC), a Data Safety Monitoring Board (DSMB) and a Clinical Endpoint Committee (CEC) will be established for this trial. The SC will ensure the scientific integrity of the trial in addition to overseeing the operational conduct. The DSMB will be constituted to oversee the safety of study participants and the CEC will adjudicate all events suggestive of the study outcomes using predefined criteria detailed in the adjudication charter.
Sample Size:	A total of 1,100 subjects is planned to be randomised (i.e., 550 per treatment group). Using the negative binomial statistical approach, the study would require 1,000 subjects in total (500 per study group) for a power of 80% and a 2-sided alpha of 0.05 to demonstrate a statistically significant rate ratio of 0.75 (i.e., 25% reduction in the composite of recurrent HF hospitalisations and CV death, between the FCM and placebo groups) assuming a recurrent event rate of 0.7 events/year for HF hospitalisations and CV death in the placebo group. The mean follow-up time is estimated to 11 month accounting for a death rate of 12%. Taking into account loss to follow-up, an overall sample size of 1,100 subjects (550 per treatment group) is planned.
Statistical Methods:	No interim analysis is planned. Analysing Recurrent Heart Failure Hospitalisations and Cardiovascular Death The crude rate of HF hospitalisations and CV deaths per 100 patient-years of follow-up will be calculated by dividing the total number of HF hospitalisations and CV deaths by the total follow-up duration of all subjects in each group. The rate ratio (95% confidence interval and p-value) between treatment groups for the composite of recurrent HF hospitalisations and CV death will be estimated for the full analysis set (FAS) using the negative binomial model. A sensitivity analysis will be performed on the per-protocol set. All secondary and other endpoints will be analysed on the FAS and all statistical tests will be performed at a 5% level. Concerning the safety data, the total number of events and number (%) of subjects with event will be presented by MedDRA system organ class and preferred term by treatment group. Further details will be specified in the Statistical Analysis Plan.

Figure 1 Flow Chart



1 Study treatment to be administered only if ID persists.
2 Performed in hospital during the AHF admission (Index hospitalisation).
3 Discharge after administration of study treatment at the discretion of the Investigator.
4 Telephone contact.
5 Outpatient clinic visit.
6 The repletion dose of study treatment will be administered based on the iron need as assessed at the baseline visit.
Notes: AHF=Acute heart failure; FCM=Ferric carboxymaltose; ID=Iron deficiency; PL=Placebo; V=Visit; W=Week.

Table 2 Schedule of Events

FLOW CHART	In-hospital		AHF Discharge	Outpatient Clinic Visits/Telephone Contact						
	V1 Screening[1]	V2 Baseline and Randomisation	Tel. Call 1	Tel. Call 2	V3	V4	V5	Tel. Call 3	V6[16]	Early Termination
		Day 0[2]	W2[3] ±3 days	W4[3] ±3 days	W6[3] ±5 days	W12[3] ±5 days	W24[3] ±10 days	W36[3] ±10 days	W52[3] ±10 days	
Written informed consent	X									
(Review of) eligibility criteria	X	X								
Demographics	X									
Medical history		X								
Physical examination		X							X	X
Body weight		X			X	X	X		X	X
Height		X								
Vital signs (Seated blood pressure, pulse rate and rhythm)		X			X	X	X		X	X
12-lead Electrocardiogram		X							X	X
Serum Ferritin, TSAT, Hb, Phosphorus	X				X	X	X		X	X
Serum pregnancy test	X[4]				X[4]	X[4]	X[4]			
Adverse events	X[5]	X	X	X	X	X	X	X	X	X
(Prior)/concomitant medications	X	X	X	X	X	X	X	X	X	X
KCCQ-12 (completion)		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6,7]	X[6]
KCCQ-12 – provisions for completion at home		X[7]					X[7]		X[6,7]	
EQ-5D		X[6]			X[6]		X[6]		X[6,7]	X[6]
HF signs and symptoms, NYHA class		X			X	X	X		X	X

FLOW CHART	In-hospital		AHF Discharge	Outpatient Clinic Visits/Telephone Contact						
	V1 Screening[1]	V2 Baseline and Randomisation	Tel. Call 1	Tel. Call 2	V3	V4	V5	Tel. Call 3	V6[16]	Early Termination
		Day 0[2]	W2[3] ±3 days	W4[3] ±3 days	W6[3] ±5 days	W12[3] ±5 days	W24[3] ±10 days	W36[3] ±10 days	W52[3] ±10 days	
Randomisation		X[8]								
Administer study treatment[9]		X[10]			X[11]	X[12]	X[12]		(13)	(13)
Check occurrence of events suggestive of study endpoints		X[14]	X	X	X	X	X	X	X	X
Biomarker blood sample[15]		X			X		X		X	X
Dispense subject identification card		X								

1 Subject screening can start at the discretion of the Investigator during the Index hospitalisation.
2 Baseline visit to be performed only if subject has ID – i.e., serum ferritin <100 ng/mL or 100 ng/mL ≤ serum ferritin ≤299 ng/mL if TSAT <20% and Hb ≥8* g/dL and ≤15 g/dL. The screening visit serum pregnancy test must also be negative in females of childbearing potential. (* Following section in italics is applicable for The Netherlands, Spain and Singapore only (**NL ES and SG only**): *The lower threshold of Hb values is set to 10 g/dL).*
3 Telephone calls/visit scheduling relative to randomisation date.
4 Only in females of childbearing potential.
5 As of the signing of informed consent.
6 KCCQ-12 and EQ-5D questionnaires to be completed before any trial related procedure performed for the visit concerned. For the telephone contacts, subjects will complete the self-administered KCCQ-12 questionnaire at home on the same day as the telephone contact.
7 Provisions to remind the subject that the KCCQ-12 questionnaire must be completed at home for the Telephone Calls 1 and 2 at Weeks 2 and 4 respectively and for Telephone Call 3 at Week 36 (and for Visit 6/Week 52).
8 Upon completion of the baseline visit procedures/assessments and after the IV drugs prescribed to treat the AHF episode have been stopped for ≥12 hours, eligible subjects will be randomised. Note: The biomarker blood sample should be drawn just prior to the administration of the first dose of study treatment.
9 Study treatment will be prepared and administered by an unblinded study personnel using black syringes and once prepared, study treatment should be administered immediately thereafter using a curtain (or similar) to maintain subject blinding. Each subject should be observed for adverse effects for at least 30 minutes following each injection of study treatment.
10 The first dose of study treatment must be administered on the same day as randomisation. To accommodate local hospital practice, the first dose of study treatment may be administered either on the same day or the day before the planned discharge day. Note that a planned overnight stay following study treatment administration does NOT fulfil the criteria of a serious adverse event unless there is a medical reason for doing this.
11 Repletion dose of study treatment to be administered based on the iron need as assessed at the baseline visit (Table 1). Dosing only in subjects for whom Hb at Week 6 (Visit 3) ≤15 g/dL. The serum pregnancy test must also be negative in females of childbearing potential. Subjects must return to the outpatient clinic for the administration of study treatment within maximally 7 days after the date when the blood sample was drawn at the respective visit.

12 Study treatment must only be administered if ID persists (i.e., serum ferritin <100 ng/mL or 100 ≤ serum ferritin ≤299 ng/mL if TSAT <20%) and Hb ≥8 g/dL* and ≤15 g/dL. The serum pregnancy test must also be negative in females of childbearing potential. Subjects must return to the outpatient clinic for the administration of study treatment within maximally 7 days after the date when the blood sample was drawn at the respective visit. (* Following section in italics is applicable for The Netherlands, Spain and Singapore only (**NL, ES and SG only**): *The lower threshold of Hb values is set to 10 g/dL.*

13 If ID persists, subject to be treated for ID according to local routine/standard practice.

14 As of the start of the administration of study treatment.

15 Biomarker blood sample to be taken in a subset of subjects of approximately 60% of randomised subjects. The first blood sample to be taken prior to the administration of study treatment.

16 Note: due to the COVID-19 pandemic situation the Investigator can perform the 52 week visit Visit 6 via remote methods (such as phone calls, video calls, etc.) to ensure at a minimum collecting subject's health status, adverse events and concomitant medications.

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LIST OF ABBREVIATIONS

AHF	Acute heart failure
ADR	Adverse drug reaction
AE	Adverse event
ARNI	Angiotensin receptor neprilysin inhibitor
BNP	Brain natriuretic peptide
CHF	Chronic heart failure
CI	Confidence interval
CEC	Clinical Endpoint Committee
CRO	Contract Research Organisation
CV	Cardiovascular
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EQ-5D	European quality of life – 5 dimensions
ES	Spain
FAS	Full analysis set
FCM	Ferric carboxymaltose
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HF	Heart failure
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Iron deficiency
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous

IWRS	Interactive web-based randomisation system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
NL	The Netherlands
NT-proBNP	N-terminal-pro-brain natriuretic peptide
NYHA	New York Heart Association
OR	Odds ratio
PP	Per-protocol set
PT	Preferred term
QoL	Quality of life
RCT	Randomised controlled trial
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Steering Committee
SG	Singapore
SOC	System organ class
TSAT	Transferrin saturation
UK	United Kingdom
VAS	Visual analogue scale
WMA	World Medical Association
w/v	Weight per volume

1. INTRODUCTION AND BACKGROUND

Two major clinical trials (FAIR-HF and CONFIRM-HF) have demonstrated that the treatment with intravenous (IV) ferric carboxymaltose (FCM) improves functional capacity, exercise tolerance, symptoms and quality of life (QoL) in stable iron deficient subjects with heart failure (HF) [1,2]. Additionally, in the secondary analysis of the CONFIRM-HF trial, the treatment with IV FCM was associated with a significant 60% reduction of the risk of hospitalisations for worsening HF during the 12 month follow-up. Moreover, the recent meta-analysis of 5 trials with IV iron therapy in patients with stable HF (including 509 subjects receiving IV iron therapy in comparison with 342 subjects receiving placebo) has shown that IV iron therapy can reduce the risk of the combined endpoint of all-cause death or/and cardiovascular (CV) hospitalisation (odds ratio (OR) 0.44, 95% confidence interval (CI) 0.30-0.64, P < 0.0001), and the combined endpoint of CV death or hospitalisation for worsening HF (OR 0.39, 95% CI 0.24-0.63, P=0.0001) [3].

Acute heart failure (AHF) constitutes a clinically and economically challenging problem. The prognosis of these patients remains poor, and so far, major clinical trials have failed to improve outcomes in these patients. The current treatment of AHF remained virtually unchanged in recent decades. iron deficiency (ID) is frequent among patients with HF and predicts poor outcome [4]. Although, there are premises that correction of ID in AHF patients could improve clinical outcomes, it has not been investigated to date.

We aim to investigate the effect of IV FCM, relative to placebo on recurrent HF hospitalisations and CV death up to 52 weeks after randomisation in iron deficient subjects hospitalised for AHF.

1.1 Background of the Disease and Treatment Options

Based on rough estimates, at least 10 million people suffer from HF in European countries [5]. The incidence of HF approaches 10 per 1,000 population after age 65, and approximately 80% of patients hospitalised with HF are more than 65 years old [6]. HF results in poor life expectancy, impaired QoL, repeated hospitalisations and is a considerable economic burden, accounting for 1–2% of health care expenditure in European countries [4]. Despite advances in its treatment, the prognosis of HF remains poor. The Euro Heart Survey showed that the in-hospital mortality of patients admitted for de novo AHF was 8.1%, and 5.8% for patients admitted for worsening HF [7]. About 50% of patients with HF will die within 4 years of the initial diagnosis, and for patients with severe chronic heart failure (CHF), approximately 50% will die within 1 year [5].

AHF has become the leading cause for hospital admissions among patients over 65 years, with unacceptably poor outcomes [8]. Despite initial stabilisation and symptomatic relief, sustained improvement in signs and symptoms of HF is difficult to maintain. In-hospital worsening of HF requiring intensification of therapy occurs in 15-20% of patients and in-hospital mortality ranges from 4-10% [7]. Post-discharge outcomes are even more

alarming; more than half of all patients will be either readmitted to the hospital or die within the first 6 months after hospital discharge [9].

The prevalence of ID is high in patients with HF as described above, most importantly both in anaemic and non-anaemic subjects. Moreover, the clear beneficial effects of IV FCM supplementation have been observed in both anaemic and non-anaemic patients with HF, suggesting that optimal iron status is crucial for the proper functioning of both haematopoietic and non-haematopoietic tissues. It should be emphasised that in spite of the critical evident role of iron for erythropoiesis, there is accumulating evidence showing that iron is needed for optimal energy metabolism of all cells [4]. Iron is essential for the transport and storage of oxygen, oxidative metabolism in the skeletal and heart muscle and the synthesis and degradation of lipids, carbohydrates, DNA, RNA [10,11]. Iron deficiency leads to mitochondrial dysfunction, and therefore unfavourable effects of depleted iron are seen predominantly in tissues of high energy demand, such as skeletal or heart muscles [4].

There is growing scientific literature describing the prevalence of ID in CHF, and individual manuscripts report that up to 50% of CHF patients may suffer from ID [12,13,14]. Patients with HF are also at risk of iron loss secondary to gastritis or ulceration caused by concomitant pharmacotherapy, and from proteinuria arising from chronic renal disease [15,16]. This decrease in iron intake respectively stores may lead to absolute ID.

In subjects with CHF, ID has been defined as serum ferritin less than 100 ng/mL (absolute ID) or serum ferritin less than 300 ng/mL with transferrin saturation (TSAT) less than 20% (functional ID) [17]. Taking into consideration the biological role of iron, it may be hypothesised that ID is a key reason for the greatly reduced exercise capacity, fatigue and breathlessness observed in these subjects. Anker et al. [18] suggested that therapeutic options to improve functional capacity are very limited and, as such, targeting abnormalities impeding oxygen transportation and/or utilisation may confer functional benefits. These hypotheses were confirmed in the FAIR-HF study with demonstrated improvements in symptomatic, functional and exercise capacity of subjects treated with FCM [1]. Several other smaller studies had shown similar benefits with the treatment of subjects using IV iron [19-22]. Beyond the improvements observed in the randomised controlled trials (RCTs) alluded to, initial evidence (in small sample sizes) suggests that iron repletion in iron deficient subjects with anaemia may also have additional benefits and improve the left ventricular dysfunction, decrease N-terminal-pro-brain natriuretic peptide (NT-proBNP) levels and inflammatory status, as measured by C-reactive protein [21].

The origin of ID in patients with HF remains unknown. Patients with HF (particularly during circulatory decompensation) have high circulating levels of pro-inflammatory cytokines, and the inflammation has been postulated by several experts as the key pathomechanism triggering the development of functional ID due to the increased liver production of hepcidin in patients with HF, similarly as in chronic kidney disease and

other chronic inflammatory disorders [23-27]. Although theoretically anticipated, until now it has not been demonstrated that ID occurring in the course of HF is linked with inflammation. On the contrary, patients with stable systolic HF developing ID have very low circulating hepcidin (without increased interleukin 6), suggesting severely depleted iron stores [28]. Also, patients with coronary artery disease undergoing coronary artery bypass graft surgery with depleted iron stores in bone marrow demonstrate low serum levels of hepcidin [29]. Finally, it has been shown that 46% of patients admitted due to AHF have extremely low circulating hepcidin level (<14.5 ng/mL), and those with low hepcidin accompanied by high circulating soluble transferrin receptor have very high 12-month all-cause mortality [4]. Provided evidence suggests that patients with HF (either when in stable or decompensated conditions) have extremely low hepcidin, which suggests the presence of profound absolute ID not related with inflammation. Such severe ID can be effectively supplemented only intravenously [3,5].

1.2 Summary of Nonclinical and Clinical Data

Geisser et al. [30] have characterised FCM as a robust and strong type iron complex (Type I) with a molecular mass of about 150,000 Daltons. The solution is a dark brown colour with a near neutral pH and a physiological osmolarity. As the product does not contain dextran it has been demonstrated to not cross react with dextran antibodies hence avoiding dextran-induced anaphylactic reactions. After IV administration, FCM is mainly found in the reticuloendothelial system of the liver, in the spleen and in the bone marrow. Since the iron is predominantly deposited in the reticuloendothelial system, and not in the parenchyma, iron induced radical forming lipid peroxidation, which takes place in the parenchyma only, is not triggered by FCM. Results from nonclinical histotoxicological investigations confirm that FCM does not cause any necroses in the liver, and no changes of toxicological importance were detected in kidney, adrenal, lung and spleen tissue following FCM administration. Except for the spleen, only a small amount of iron is found in the organs, which is due to high iron complex stability.

A clinical pharmacokinetics study [31,32] using positron emission tomography demonstrated a fast initial elimination of radioactively labelled iron $^{52}Fe/^{59}Fe$ FCM from the blood, along with rapid transfer to the bone marrow and rapid deposition in the liver and spleen. At 8 hours after administration, 5-20% of the injected amount was still in the blood. The projected calculated half-life of terminal elimination was about 16 hours, in comparison to 3 to 4 days for iron dextran and 6 hours for iron sucrose. A further Phase 2 study in subjects with ID anaemia demonstrated a monoexponential elimination pattern with a half-life of terminal elimination in the range 10 to 18 hours. There was negligible renal elimination. In this and another registration study, total serum iron returned to the normal range within 3 and 7 days allowing for a weekly dosing schedule. In general, clinical safety and efficacy studies have been conducted in numerous settings that are representative of underlying diseases that may lead to ID i.e., diseases with increased inflammatory status that impairs iron absorption as well as diseases with large losses of iron that cannot be compensated via dietary iron.

Since the developmental international birth date, more than 7,000 subjects are known to have been exposed to FCM with at least one dose in more than 35 completed prospective, interventional clinical studies. Across various clinical studies, replenishment of iron stores has been consistently observed. Markers of ID have included both TSAT and serum ferritin. In subjects with more severe or prolonged ID that has led to anaemia, correction of ID using FCM has consistently resulted in medically significant increases in haemoglobin (Hb) values (correction of anaemia). This improvement was usually seen within 2 weeks. In addition to the correction of laboratory parameters, iron replacement therapy has demonstrated significant improvements in subject QoL and functional status. Ferric carboxymaltose was well tolerated by study participants. In the completed clinical studies, up until the 1 January 2015, approximately 50% of the subjects experienced at least 1 treatment-emergent adverse event (AE), and events considered related to treatment occurred in just over 17% of subjects who received FCM. The most commonly reported adverse drug reactions (ADRs) in the FCM group were nausea, injection/infusion site reactions, hypophosphataemia, headache, flushing, dizziness, and hypertension.

In relation to laboratory parameters recorded in clinical studies, no consistent pattern of clinically meaningful changes requiring intervention have been observed. However, mild and transient changes of liver enzymes, such as aspartate aminotransferase and alanine aminotransferase, gamma-glutamyl transferase and alkaline phosphatase, have been reported in some studies. A transient decrease in blood phosphorus levels was frequently observed. The nadir occurred approximately 2 weeks after dosing and resolved without treatment in most subjects within the follow-up period of up to 12 weeks. Severe hypophosphataemia (i.e., <0.3 mmol/L) was observed in very few cases, and was of short duration.

No formal interaction studies have been performed. Except for the reduced uptake of oral iron administered in parallel with parenteral iron, no interactions with other medications are known.

The first marketing authorisation for FCM was received in July 2007, and as of 1 January 2015, FCM has received marketing authorisation in a total of 63 countries worldwide. The total exposure of patients since the introduction of FCM into the market up to December 2014 corresponded to more than 2,000,000 patient-years. The total number of spontaneous and solicited adverse drug experience cases reported is considered small with respect to the overall drug exposure. Post-marketing reports up to December 2014 confirm the known AE profile and the positive benefit/risk ratio of FCM.

Please see the Investigator’s Brochure for further details.

2. RATIONALE

Currently there are 8 studies of varying sizes performed using IV iron in stable HF subjects, and 2 of these studies using IV FCM conducted as placebo-controlled, double-blinded studies [1,2]. These two RCTs have provided evidence, that relative to placebo, the correction of ID with IV FCM improves clinical functional capacity, symptoms, clinical findings related to HF and QoL. In addition, IV FCM was well tolerated.

To date, no data exists concerning the impact of IV FCM on recurrent HF hospitalisations and CV death in a HF population with ID who have recently stabilised after an AHF episode. The intervention is planned in subjects with diagnosed ID at the time of randomisation and left ventricular ejection fraction (LVEF) <50% demonstrated at any time within 12 months prior to randomisation. In this trial, it is planned to administer the first IV dose of FCM/placebo just prior to discharge for the AHF episode. Subjects will be followed for 52 weeks and study treatment will be administered at Week 6 based on the iron need as assessed at the baseline visit, and at Weeks 12 and 24 if ID persists at these time points. Recent observational data from Jankowska et al. [33] in subjects with systolic CHF, suggested that ID constitutes a strong independent predictor of unfavourable outcome proposing that iron supplementation may be considered as a therapeutic approach in CHF subjects to improve outcome. In this observational study, a distinct difference in survival curves in favour of non-iron deficient subjects was observed within the first 6-12 months. After 12 months the difference between iron deficient and non-iron deficient subjects remained stable.

Study Design Rationale

This is a randomised, double-blind, placebo-controlled trial. The 52 weeks observation period following randomisation is considered appropriate to investigate the primary endpoint of recurrent HF hospitalisations and CV death. To evaluate the effect of IV FCM in iron deficient subjects with AHF, subjects will be enrolled during a hospital stay (Index hospitalisation) after the acute care treatment of the index event has been stabilised.

All subjects will continue to receive their established standard therapy for HF and medical emergencies will be treated according to local routine. Placebo-treatment will be used for blinding reasons of IV FCM treatment, and as such does not bear any additional risk to the subject. Given that there is no proven effective intervention for the condition under investigation in the AFFIRM-AHF trial, the use of a placebo arm is considered ethically justified.

For this trial, the same treatment algorithm was selected to be used as that implemented in an RCT with IV FCM in stable CHF subjects [2]. First treatment will be administered in the hospital prior to discharge. Over the 52 weeks following randomisation, the collected endpoints will focus on important events for this subject population (hospitalisations, mortality and QoL) that directly impacts the subjects and the health care system.

A Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) will be constituted to protect the safety of study participants and a Clinical Endpoint Committee (CEC) will be established to ensure robust assessment of all events suggestive of the primary study endpoint.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to evaluate, relative to placebo, the effect of IV FCM on repeated HF hospitalisations and CV death.

3.2 Secondary Objectives

The secondary objectives are to evaluate, relative to placebo, the effect of IV FCM on:

- HF hospitalisations, CV hospitalisations, CV mortality and all-cause mortality
- Quality of life and New York Heart Association (NYHA) Classification
- Tolerability and safety

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

The AFFIRM-AHF trial is multicentre, randomised, double-blind, prospective, parallel-group, placebo-controlled, trial with a fixed follow-up of 52 weeks after randomisation per subject. The Schedule of Events is shown in Table 2 and Figure 1.

4.1.1 Screening Visit

The AHF hospitalisation will be considered as the Index hospitalisation. The screening visit will be performed in-hospital. The screening visit process can be summarised as follows:

- Subjects who have been hospitalised for an AHF episode will be screened to determine potential eligibility to participate in the AFFIRM-AHF trial.
- The Investigator will obtain written informed consent from potentially eligible subjects before any trial-related procedure is performed.
- As of the date of informed consent for each subject, the sites will document in the electronic case report form (eCRF) all AEs and changes/additions made to concomitant medications. SAEs will be reported as they occur but no later than 24 hours after the Investigator's awareness of the event.
- In potentially eligible subjects, a blood test will be drawn, which will be analysed locally, to determine if the subject is iron deficient and if the Hb ≥8 g/dL* and ≤15 g/dL. Iron deficiency is defined as serum ferritin <100 ng/mL, or 100 ng/mL ≤ serum ferritin ≤299 ng/mL if TSAT <20%. The assays to be performed are: serum ferritin, TSAT and Hb. In addition, serum phosphorus levels analysed locally from the same blood draw will be documented in the eCRF.
- During the same blood draw, a serum pregnancy test will be taken for females of childbearing potential.

*Following section in italics is applicable for The Netherlands, Spain and Singapore only (**NL, ES and SG only**):

The lower threshold of Hb values is set to 10 g/dL.

4.1.2 Baseline Visit, Randomisation and Administration of the First Dose of Study Treatment

The baseline visit process/procedures can be summarised as follows:

- Upon receipt of the screening visit blood test results, the baseline visit will be performed for subjects in whom ID is confirmed and for whom the baseline Hb ≥8 g/dL* and ≤15 g/dL. In addition, for females of childbearing potential, the serum pregnancy test must be negative. The Investigator will perform/complete the baseline procedures/assessments as shown in Table 2.

  *Following section in italics is applicable for The Netherlands, Spain and Singapore only (**NL, ES and SG only**):

  The lower threshold of Hb values is set to 10 g/dL.

- In a subset of subjects samples for determination of blood biomarkers will be retained.

- Upon completion of the baseline visit procedures/assessments and after the IV drugs prescribed to treat the AHF episode have been stopped for ≥12 hours, eligible subjects will be randomised using a validated centralised procedure (interactive web-based randomisation system (IWRS)) to either FCM or placebo. Study treatment must be administered on the same day as randomisation. To accommodate local hospital practice, the first dose of study treatment may be administered either on the same day or the day before the planned discharge day. Note that a planned overnight stay following study treatment administration does NOT fulfil the criteria of an SAE unless there is a medical reason for doing this.

- Study treatment will be prepared and administered by unblinded study personnel who will otherwise not be involved in any study assessments for the subject concerned other than assessment and interpretation of post-randomisation laboratory test results.

- The dose of study treatment to be administered will be done following the instructions in Table 1. Each subject should be observed for adverse effects for at least 30 minutes following each injection of study treatment. Thereafter, the subject may be discharged from hospital, at the discretion of the Investigator.

4.1.3 Post-Randomisation Visits

The post-randomisation subject contacts can be summarised as follows:

- Subjects will return to the outpatient clinic at 6, 12, 24 and 52 weeks after randomisation.

Note: due to the COVID-19 pandemic situation the Investigator can perform the 52 week visit (Visit 6) via remote methods (such as phone calls, video calls, etc.) to ensure collecting at a minimum subject's health status, AEs and concomitant medications.

- During the outpatient visits, the Investigator will perform the procedures/assessments as shown in Table 2 for each respective visit.

- At Weeks 6 (Visit 3), 12 (Visit 4), 24 (Visit 5) and 52 (Visit 6) a blood test, which will be analysed locally, will be drawn. The assays to be performed are: serum ferritin, TSAT and Hb. If ID persists and Hb ≥8* g/dL and ≤15 g/dL at Weeks 12 (Visit 4) and 24 (Visit 5), the dose of study treatment to be administered will be determined as shown in Table 1. In addition, serum phosphorus levels analysed locally from the same blood draw will be documented in the eCRF.

  *Following section in italics is applicable for The Netherlands, Spain and Singapore only (**NL, ES and SG only**):

  The lower threshold of Hb values is set to 10 g/dL.

- During the same blood draw (except at Week 52 (Visit 6)), a serum pregnancy test will be taken for females of childbearing potential.

- At Week 6 (Visit 3) the repletion dose of study treatment will be administered based on the iron need as assessed at the baseline visit (Table 1) and only in subjects for whom Hb at Week 6 (Visit 3) ≤15 g/dL. For females of childbearing potential, the serum pregnancy test must be negative.

- Subjects for whom an administration of study treatment is necessary during an outpatient clinic visit, will be requested to return to the outpatient clinic for the administration of study treatment maximally 7 days after the date when the blood sample was performed for the respective outpatient clinic visit. For females of childbearing potential, the serum pregnancy test must be negative.

- In a subset of subjects samples for determination of blood biomarkers will be retained at Weeks 6 (Visit 3), 24 (Visit 5) and 52 (Visit 6).

- Study treatment will be prepared and administered by unblinded study personnel who will otherwise not be involved in any study assessments for the subject concerned other than assessment and interpretation of post-randomisation laboratory test results.

- The dose of study treatment to be administered will be determined following the instructions in Table 1. Each subject should be observed for adverse effects for at least 30 minutes following each injection of study treatment. Thereafter, the subject may leave the outpatient clinic at the discretion of the Investigator.

- The site will contact the subject by telephone at Week 2 (Telephone Call 1), Week 4 (Telephone Call 2), and Week 36 (Telephone Call 3), after randomisation to enquire about the subject's health status and enquire if the subjects experienced a deterioration of their condition or if they were hospitalised since the last visit contact and/or if there were changes made to their concomitant treatments. The latter will be reported in the eCRF. The subjects will be requested to complete the Kansas City Cardiomyopathy Questionnaire (KCCQ)-12 questionnaire at home on the same day as the Week 2, Week 4 and Week 36 telephone call. The subjects will be instructed to return the completed questionnaires at the following out-patient clinic Visit. Adverse events will also be reported in the eCRF. If the subject reports a hospitalisation, the Investigator must report the SAE as per the protocol requirements (see Section 10).

- If ID persists at Week 52 (Visit 6), the Investigator will treat the ID according to local routine/standard practice.

The FCM and placebo solutions differ in appearance. Hence, unblinded study personnel not otherwise involved in any study assessments (other than assessment and interpretation of post-randomisation laboratory test results) will be responsible for preparing and administering the study treatment injections in black syringes and using a curtain (or similar) to maintain subject blinding. The unblinded study personnel will ensure that the subject is not able to observe the preparation and administration of the study treatment injections. The unblinded physician will review the laboratory test results at the respective follow-up visits to determine if ID persists and hence the need to administer study treatment (or not).

4.2 Duration of Subject Participation and Study

The duration of subject participation is 52 weeks (i.e., 12 months) as of randomisation. The end of study is defined as the Last Subject Last Visit.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Number of Subjects

In total, 1,100 subjects will be randomised from approximately 100 sites. For a detailed justification of the sample size please refer to Section 12.2.

5.2 Inclusion Criteria

Investigators must maintain a screening log of all potential study candidates that includes limited information about the potential candidate, date, and outcome of the screening process (e.g., enrolled into study, reason for ineligibility, or refused to participate). The following inclusion criteria must be met for each subject:

1. Currently hospitalised for an episode of AHF where AHF was the primary reason for hospitalisation. All of the following (i.e., items a to d) must apply:

    a. Upon admission for the AHF episode, persistent dyspnoea at rest in a recumbent sitting position (30-45°) or with minimal exertion

    b. Upon or during the AHF admission, at least two (2) of the following clinical findings were present:

        i. Congestion on chest x-ray

        ii. Rales on chest auscultation

        iii. Oedema ≥1+ on a 0-3+ scale, indicating indentation of skin with mild digital pressure that requires 10 or more seconds to resolve in any dependent area including extremities or sacral region

        iv. Elevated jugular venous pressure (≥8 cm H_2O)

    c. Natriuretic peptide levels, measured ≤72 hours of the AHF admission must have been:

        i. Brain natriuretic peptide (BNP) ≥400 pg/mL or NT-proBNP ≥1,600 pg/mL or

        ii. BNP ≥600 pg/mL or NT-proBNP ≥2,400 pg/mL for subjects presenting with atrial fibrillation when the blood sample was taken

        iii. For subjects treated with an angiotensin receptor neprilysin inhibitor (ARNI) in the previous 4 weeks prior to randomisation only NT-proBNP values should be considered

    d. AHF episode treated with minimally 40 mg of IV furosemide (or equivalent IV loop diuretic defined as 20 mg of torasemide or 1 mg of bumetanide)

2. Subject is iron deficient defined as serum ferritin <100 ng/mL or 100 ng/mL ≤ serum ferritin ≤299 ng/mL if TSAT <20%.

3. Left ventricular ejection fraction <50% (assessed and documented within 12 months prior to randomisation)

4. Male or female aged ≥18 years old.

5. Subject (or legally acceptable representative)* has provided the appropriate written informed consent. Subject must provide written informed consent before any study-specific procedures are performed.

*Following section in italics is applicable for The Netherlands only (**NL only**):

The option that legally accepted representatives of subjects can sign the written informed consent is not valid for sites in The Netherlands.

5.3 Exclusion Criteria

The following exclusion criteria must NOT be present for each subject:

1. Dyspnoea due to non-cardiac causes such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, acute bronchitis, pneumonia, primary pulmonary hypertension).

2. Temperature >38°C (oral or equivalent), active infective endocarditis, sepsis, systemic inflammatory response syndrome, or any other active infection requiring anti-microbial treatment at any time during an Index hospitalisation. (Note that it does NOT include short-term prophylactic administration of antibiotics or short-term temperature elevation at admission which is no longer present at the time point of discharge/randomisation).

3. Documented restricted amyloid myocardiopathy, or acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy. (Note that it does NOT include restrictive mitral filling patterns seen on Doppler echocardiographic assessments of diastolic function).

4. Clinical evidence of acute coronary syndrome, transient ischemic attack or stroke, within the last 30 days prior randomisation.

5. Severe valvular or left ventricular outflow obstruction disease needing intervention.

6. Coronary-artery bypass graft, cardiac resynchronisation therapy device implantation, percutaneous intervention (e.g., cardiac, cerebrovascular, aortic; diagnostic catheters are allowed) or major surgery that led to significant blood loss, including thoracic and cardiac surgery, within the last 3 months prior to randomisation.

7. Subject has a body weight <35 kg at randomisation.

8. Subject at an immediate need of transfusion or with a Hb <8 g/dL* or with a Hb >15 g/dL.

9. Subjects on treatment for Vitamin B12 and/or serum folate deficiency. Note: Use of Vitamin B12 and folic acid as supplement therapy (not for deficiency treatment) is permitted.

10. Subject with a known anaemia not attributed to ID (e.g., other microcytic anaemia) or with an evidence of iron overload (e.g., haemochromatosis) or disturbances in the utilisation of iron.

11. Subject has known hypersensitivity to any of the study products to be administered or known serious hypersensitivity to other parenteral iron products.

12. Subject with known severe allergies including drug allergies, history of severe asthma, eczema or other atopic allergy and in subjects with immune or inflammatory conditions (e.g., systemic lupus erythematosus, rheumatoid arthritis).

13. History of erythropoietin stimulating agent, IV iron therapy, and/or blood transfusion in previous 3 months prior to randomisation.

14. Oral iron therapy at doses >100 mg/day in previous 4 weeks prior to randomisation. Note: Ongoing use of multivitamins containing iron <75 mg/day are permitted.

15. Currently receiving systemic chemotherapy and/or radiotherapy.

16. Renal dialysis (previous, current or planned within the next 6 months).

17. Subject has known active malignancy of any organ system, i.e., clinical evidence of current malignancy or not in stable remission for at least 3 years since completion of last treatment with exception of non-invasive basal cell carcinoma, squamous cell carcinoma of the skin or cervical intra-epithelial neoplasia.

18. Terminal illness other than HF with expected survival <12 months.

19. Chronic liver disease (including active hepatitis) and/or alanine transaminase or aspartate transaminase above 3 times the upper limit of the normal range.

20. Subjects with known hepatitis B surface antigen positivity and/or hepatitis C virus ribonucleic acid positivity.

21. Subject previously randomised into this study. Note: Subjects may be rescreened but when rescreened, all tests must fall inside the maximum specified screening windows for each criterion.

22. Subject is currently enrolled in or has completed any other investigational device or drug study <30 days prior to screening, or is receiving other investigational agent(s).

23. Subject is pregnant (e.g., positive human chorionic gonadotropin test) or breast feeding.

24. If of childbearing potential, subject is not using adequate contraceptive precautions. Subject must agree to use adequate contraception during the study and for 1 month after the last dose of study treatment. A highly effective method of birth control must be used.

25. Subject has a history of drug or alcohol abuse within 2 years prior to screening.

26. Subject has a significant medical condition(s), anticipated need for major surgery during the study, or any other kind of disorder that may be associated with increased risk to the subject, or may interfere with study assessments, outcomes, or the ability to provide written informed consent or comply with study procedures, in the Investigator's opinion.

*Following section in italics is applicable for The Netherlands, Spain and Singapore only (**NL, ES and SG only**):

The lower threshold of Hb values is set to 10 g/dL.

5.4 Withdrawal of Subjects

5.4.1 Withdrawal of Subjects from Study Drug

Study drug must be stopped if the subject experiences any kind of hypersensitivity reaction related to the study drug during administration. The subject concerned will remain under follow-up and the subsequent visits should be performed in accordance with the protocol schedule. Whether the subject should receive additional doses of study treatment will be discussed with the Medical Monitor and will be decided on a case by case basis. If study drug is stopped prematurely for any one subject, the subject concerned will not be replaced.

Subjects may be withdrawn from the study drug if in the opinion of the Medical Monitor or the Investigator there would be a risk to the subject's safety if they received any further dose of study drug.

Following section in italics is applicable for The Netherlands, Spain and Singapore only (**NL, ES and SG only**):

Subjects enrolled in the study with Hb levels that are falling below the threshold of 10 g/dL during the study will need to be withdrawn from further study treatment dosing.

If study treatment is stopped prematurely for a subject, follow-up for the subject concerned should continue in accordance with the protocol schedule. The discontinuation of study treatment is mandatory in circumstances that therapies or treatments listed in Section 7.7.2 as restricted need to be applied to the subjects for general health reasons. Discontinuation of study treatment is also mandatory in the case a subject enrolled into the study is getting pregnant (see Section 10.3.3 for reporting instructions).

The reason for study-drug discontinuation and the date must be recorded on the appropriate page of the eCRF. The follow-up of these subjects should continue in accordance with the protocol schedule.

5.4.2 Withdrawal of Subjects from Follow-up

Subjects may voluntarily withdraw their participation from the trial at any time without having to provide a reason or a subject may be withdrawn from follow-up at the Investigator's discretion if it is in the subject's best interest. The reason(s), including the primary reason for withdrawal from follow-up, if provided by the subject, will be recorded in the eCRF. Although a subject is not obliged to give her/his reason(s) for discontinuing trial participation prematurely, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. If the subject does not wish to provide a reason, the source documents and the eCRF should document the reason for discontinuation as "withdrawal by subject". Whenever possible, the Investigator should request the subject to return for a clinic assessment at the time of or soon after discontinuation from follow-up. The Investigator is required to make every effort possible to follow the subject concerned for survival and hospitalisation after discontinuation of follow-up on the condition that the subject has not withdrawn consent to do so.

If subjects refuse to return to the outpatient clinic for the scheduled visits, all reasonable efforts should be made to contact the subject by telephone at the time point of the scheduled visits. In such situations and unless the subject withdraws informed consent for further participation in the trial, all randomised subjects who withdraw from follow-up visits prematurely will continue to be followed for the occurrence events suggestive of the study outcomes.

It is vital to obtain follow-up data on any subject withdrawn because of an AE. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures. If a subject is discontinued due to an AE, the event should be followed by the Investigator through contact with the subject until resolution or stabilisation has occurred. All AEs should be followed until resolution, stabilisation or the subject is lost to follow-up and cannot be contacted.

Reasons for discontinuations will be documented in the eCRFs. Subjects who discontinue prematurely will not be replaced.

5.5 Rescreening of Subjects

A subject can only be randomised once in the AFFIRM-AHF trial. If a randomised subject withdraws consent for further follow-up, the subject concerned cannot be rescreened. However, a subject who fails to meet the protocol selection criteria and who was not randomised during the initial Index hospitalisation may be reconsidered for participation during any subsequent hospitalisation for AHF.

5.5.1 Subject Rescreening During the Same Index Hospitalisation

If during the initial Index hospitalisation, the blood test results and/or ejection fraction measurement are outside the criteria defined in the study protocol, the diagnostic tests may be repeated once during the same Index hospitalisation. If the second blood test results and/or second ejection fraction measurement are still outside the limits set by the study protocol, the subject will not be eligible to participate.

5.5.2 Subject Rescreening

Subjects determined as being ineligible during the initial Index hospitalisation may be rescreened for participation at a subsequent hospitalisation(s) for worsening HF. The subject(s) concerned will be considered as a de-novo screening and the subsequent hospitalisation for worsening HF will be considered as the Index hospitalisation. The subject must sign a new informed consent form (ICF) and will be allocated a new subject identification number. The screening and baseline visits must be performed in accordance with Table 2 and with Section 5.5.1.

6. RANDOMISATION, BLINDING AND UNBLINDING PROCEDURES

6.1 Randomisation

All subjects enrolled must be identifiable throughout the study. The Investigator will maintain a list of subject numbers and subject names to enable records to be found at a later date.

Numbered study treatment packs will contain either FCM solution or placebo (i.e., normal saline) according to a computer generated randomisation plan.

Each eligible subject will be randomised to either FCM or placebo using a validated centralised procedure (IWRS) that automates the random assignment of treatment groups to randomisation numbers. Subject randomisation (1:1) will be determined by a minimisation algorithm including a random variable and accounting for the following stratification factors: sex, age (<70 years/≥70 years), HF aetiology (ischemic/ non-ischemic), HF duration (newly diagnosed at Index hospitalisation/known documented HF prior to Index hospitalisation), country and centre. The system will allocate study treatment pack number(s) which should be used for the subject concerned. Details on how to randomise a subject will be found in the respective user manual.

The randomisation plan will be kept strictly confidential, accessible only to authorised persons, until the time of unblinding. If a subject discontinues from the study, neither the subject identification number nor the allocated study treatment pack numbers will be reused, and the subject will not be allowed to be re-randomised in the study.

6.2 Blinding

This is a double-blind trial with randomisation concealment and neither the Investigator, the subject nor Sponsor (or representative) will be aware of the administered study treatment to each subject. The Vifor Pharma Safety Department will have access to the randomisation codes as will investigational sites should the need to unblind a subject arise.

As the FCM and placebo solutions differ in appearance and the study treatment boxes will not be blinded, unblinded study personnel not involved in any study assessments (other than assessment and interpretation of post-randomisation laboratory test results) will be responsible for handling the study treatment boxes, and preparing and administering the study treatment injections in black syringes and using a curtain (or similar) to maintain subject blinding. Unblinded personnel will make sure the subject is not able to observe the preparation of study treatment injections.

Post-baseline iron values should be seen only by the unblinded study physician, who will then be responsible for evaluating the parameters. This physician must review the parameters to confirm the subject well-being and follow guidance per Section 10.2.6.

6.3 Unblinding

In an emergency situation where knowledge of a subject's study treatment allocation must be present in order to determine the further medical management of the subject concerned, or if knowledge of a subject's treatment allocation is required for safety regulatory reporting purposes, the blinded Investigator or the Sponsor pharmacovigilance officer, respectively (as appropriate) will have access to the study treatment code for the subject concerned via the secure, web-based trial-specific treatment allocation system. Instructions for access (which is password protected) and use may be found in the respective user manual. All information (i.e., the name of the person who has accessed the treatment code, the reason, date and time and subject for whom the code was accessed) concerning study treatment code access will be tracked and stored in the web-based system.

If a study treatment code is broken, the subject concerned must discontinue study treatment. Further medical management is at the discretion of the Investigator. However, clinical status permitting, all remaining planned outpatient clinic visits and telephone calls must be completed in accordance with the protocol schedule unless the subject refuses further follow-up.

7. STUDY TREATMENTS

7.1 Dosage Forms/Formulation

All investigational medicinal products to be used in this study have been manufactured in accordance with current Good Manufacturing Practice (GMP). FCM will be provided by Vifor Pharma.

7.1.1 Formulation of Ferric Carboxymaltose

Active Ingredient:	Ferric carboxymaltose
Strength:	Sterile FCM solution as a 5% weight/volume (w/v) iron solution in water for injection
Excipients:	Sodium hydroxide, hydrochloric acid, water for injections
Appearance:	Dark brown, non-transparent aqueous solution
Dosage Form:	10 mL vials containing 500 mg iron per vial
Manufacturer:	Vifor Pharma – Vifor (International) Inc., Switzerland
Storage:	As indicated on the label

7.1.2 Formulation of Normal Saline

Normal saline will be provided by Vifor Pharma for this study.

Active Ingredient:	NaCl (normal saline)
Strength/packaging:	10 mL container with 10 mL normal saline
Excipients:	Water for injections
Appearance:	Clear aqueous solution
Dosage Form:	0.9% w/v NaCl as sterile solution in water for injections
Manufacturer:	B. Braun Melsungen AG
Storage:	As indicated on the label

7.2 Study Treatment Dosage and Administration

7.2.1 Treatment Arms

Eligible subjects will be randomised (1:1) to either FCM or placebo using a validated centralised procedure (IWRS).

7.2.2 Dosing and Administration Guidelines

The dose of study treatment to be administered will be determined using the subject's body weight and Hb values based on a repletion and maintenance dosing scheme. Subjects will be administered study treatment as an undiluted bolus IV injection - a 10-mL vial of FCM contains 500 mg iron. The individual dose requirements (in mL) per visit are detailed in Table 1. The doses of study treatment administered at Visits 2 and 3 are considered the repletion phase and any subsequent administrations (if ID persists) will be considered the maintenance phase. All administrations, including duration of injection, will be documented in the site source data and in the eCRF. Each administration of study treatment will be documented in the treatment accountability log kept by the unblinded person on site.

The IV bolus injection will be done using a black syringe. A curtain (or similar) will be used in addition to ensure that blinding of the subject is maintained. Injections will have a volume of 20 mL (1,000 mg iron or normal saline) or 10 mL (500 mg iron or normal saline) depending on the subject's Hb value and body weight.

In case a site has local regulations that prevent the use of a black syringe then the investigational site needs to provide an alternative acceptable procedure that will maintain the blind, whilst satisfying their local procedures. This alternative procedure must receive approval by the Sponsor on a site-by-site basis.

The following describes the procedure for the preparation and administration of study treatment.

7.2.2.1 Preparation of Study Treatment

Study treatment must be prepared by an unblinded member of the site study team using black syringes. The volume of study treatment to administrate must follow the instructions in Table 1. When preparing the FCM solution, the vials should be visually inspected for sediment and damage before use and only those containing sediment-free, homogeneous solution should be used. Once prepared, study treatment should be administered immediately thereafter.

7.2.2.2 Administration of Ferric Carboxymaltose and Placebo

Study treatment should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured.

Unblinded study personnel will administer study treatment. He/she should apply tourniquet, identify a suitable vein, disinfect the injection site and perform the venous puncture. It is recommended to use a blue catheter 22 G or pink catheter 20 G and secure it with duct tape. The use of blue butterfly needle is possible but a curtain (or similar) must be used to maintain blinding of the subject during the administration of study treatment.

After the venous puncture is performed, the correct positioning of the needle (within the vein) can be checked by flushing with 10 mL NaCl 0.9%. Thereafter, the study personnel should then connect the syringe containing the study treatment to the needle and slowly inject the study treatment over at least 5 minutes for the 500 mg dose and over at least 15 minutes for the 1,000 mg dose).

After administration, the vein should then be flushed with 5-10 mL saline. Each subject should be observed for adverse effects for at least 30 minutes following each injection.

Since FCM has a physiological pH, pain at the injection site is unlikely, therefore caution should be exercised to avoid paravenous injections. The choice of an appropriate needle (i.e., a blue catheter 22 G or pink catheter 20 G) for the IV access should minimise the potential risk of a paravenous injection of FCM or placebo.

The administration of study treatment should be discontinued immediately if swelling (paravenous injection) is observed at or around the injection site which can cause irritation and a brown discolouration of the skin which can be long-lasting. Please refer to Section 7.6 for more details. No rinsing or pressure bandage should be used, in order to prevent distribution and extension of extravasations.

7.3 Package and Labelling

Study drug will be supplied to each site already packaged and labelled. The packaging and labelling of study treatment will be performed according to GMP and GCP (Good Clinical Practice). In addition, the content of the labels to be affixed on the study treatment packs will be in accordance with local regulations for clinical trials. Each study treatment pack and its content will be identified by a treatment number. Once allocated to a subject, the content from a specific study treatment pack should not be used for another subject.

7.4 Study Treatment Allocation

Each eligible subject will be randomised to either FCM or placebo using a secure validated centralised (IWRS) system. The system will allocate a study treatment pack number which should be used for the subject concerned. Details how to randomise a subject will be found in the respective user manual. Numbered study treatment packs will contain either FCM solution or placebo (normal saline) according to a computer generated randomisation plan.

7.5 Site Supply, Storage, Accountability

7.5.1 Site Supply

Once a site has been approved to receive study treatment, the site will be supplied with an initial stock of study treatment. The need for treatment resupply will be assessed on a regular basis taking into account the number of subjects enrolled, and the number of subjects in screening at the site.

7.5.2 Storage

Study treatment must be stored in a locked and temperature controlled area. Each site should have a thermometer that records minimum and maximum temperatures daily. Maintenance of a temperature log is mandatory. The log should be updated by site personnel daily. This log must be available for review by the Monitor during on-site monitoring visits.

7.5.3 Accountability

The unblinded study personnel at each site is responsible for study treatment supplies. The study personnel will ensure that adequate records of the receipt, preparation, administration and return of the study treatment are kept and that the study treatment is used only for subjects enrolled in the study. All data regarding the study treatment (including kit and batch numbers) must be recorded in the eCRF and on any other relevant forms provided.

Each study site will maintain a treatment inventory/dispensing record for all treatments dispensed and returned. At the end of the study, 1 copy of the treatment inventory/dispensing record should be sent to the Sponsor for the central study file. The original will be kept in the site files.

After completion of the study, or if it is prematurely terminated, all unused materials will be returned to the Sponsor. The decision to destroy study treatment at site must be made by the Sponsor. If the study treatment is destroyed at site, the Investigator will forward the certificate of destruction to the Sponsor.

7.6 Study Treatment Dose Modification

If extravasation is noted during administration of study treatment, the administration should be ceased immediately. Study treatment administration may be completed using a different injection site to complete the required dosage.

7.6.1 Procedures for Overdose

If an inadvertent overdosing of a subject (e.g., by a calculation error of the required iron dose) is detected, this will be reported as a special situation. If associated with any signs/symptoms, this will be reported as an AE (see Section 10).

Post-baseline iron parameters will be assessed by the unblinded Investigator at each visit using the local laboratory. In the case of iron accumulation the Investigator at the site will initiate corrective measures according to local guidelines for treatment of iron overload.

7.7 Prohibited Therapy and Concomitant Treatment

All medications and treatments prescribed for a subject at the time of or during screening, and all additional medications or dose changes made during follow-up, are considered to be concomitant treatments. In addition, all treatments prescribed up to at least 3 months

prior to informed consent must also be documented in the eCRF, irrespective if the treatment is still on-going or not. This includes the treatments prescribed to treat the AHF episode during the Index hospitalisation.

7.7.1 Basic Regimen

In this trial, study treatment (i.e., FCM or placebo) is given in addition to the basic HF treatment regimen. Anti-coagulants and/or platelet aggregation inhibiting drugs may be used according to local routine. No trial-specific dietary requirements are mandated by the protocol and other medications to treat concurrent diseases can be prescribed as required provided that the restrictions given in Section 7.7.2 are adhered to.

As of randomisation, the aim should be to keep the prescribed basic regimen for HF as stable as the subject's clinical presentation permits over the 52-week follow-up period. However, if symptoms or signs develop which suggest a worsening of HF, the management and treatment of subjects is at the discretion of the Investigator.

Any other clinically relevant diagnosis or finding(s) which develops or worsens during the subject's participation in the trial may be treated as indicated, provided that the restrictions given in Section 7.7.2 are observed. Any new clinically relevant symptom, diagnosis or finding must be reported as an event on the appropriate SAE or AE report form (see Section 10).

7.7.2 Concomitant Treatment Restrictions

The following therapies or treatments must not be given, or must not be performed, concurrently with study treatment (if needed, subject has to be withdrawn from study treatment):

- Immunosuppressive or myelosuppressive therapy
- Erythropoietin
- Oral or IV iron therapy (other than study medication). Note: Ongoing use of multivitamins containing iron <75 mg/day are permitted.
- Blood transfusion
- Surgery that may result in significant blood loss (>100 mL or >1 g/dL Hb)
- Renal dialysis
- Heart transplant

7.7.3 Treatment in the Case of an Emergency

The Investigator is responsible for ensuring that appropriate processes, procedures and expertise are in place to cope with medical emergencies that occur during the trial.

Medical emergencies should be treated according to local routine. Continuation of the study treatment is at the discretion of the Investigator beside in cases of an emergency that involves any kind of hypersensitivity reaction related to the study drug during administration. The latter case will be discussed with the Medical Monitor and a case by case decision will be made, whether the subject should receive additional doses of study treatment (Section 5.4.1). The guidelines and restrictions given in Section 7.7.2 must be adhered to as long as the subject is still on study treatment.

An emergency situation constitutes an immediately reportable SAE (see Section 10).

8. RISKS/PRECAUTIONS

8.1 IV Iron Risks

Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be fatal. Therefore, facilities for cardiopulmonary resuscitation must be available. If allergic reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Hypersensitivity reactions have been reported after previously uneventful doses of any parenteral iron complexes, including FCM. Each subject should be observed for adverse effects for at least 30 minutes following administration of the study treatment.

In subjects with liver dysfunction, parenteral iron should only be administered after careful benefit/risk assessment. Parenteral iron administration should be avoided in subjects with hepatic dysfunction where iron overload is a precipitating factor, in particular porphyria cutanea tarda. Careful monitoring of iron status is recommended to avoid iron overload.

Parenteral iron must be used with caution in cases of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that the administration of FCM be stopped in subjects with ongoing bacteraemia. In subjects with chronic infection, a benefit/risk evaluation has to be performed, taking into account the suppression of erythropoiesis (due to chronic infection).

Paravenous leakage must be avoided because leakage of FCM solution at the injection site may lead to irritation of the skin and potentially long-lasting, brown discolouration at the site of injection. In the event of paravenous leakage, administration of FCM must be stopped immediately. Study treatment administration may be completed using a different injection site to complete the required dosage.

8.2 Ferric Carboxymaltose

One mL of undiluted FCM solution contains up to 5.5 mg (0.24 mmol) of sodium. This has to be taken into account in subjects on a sodium-controlled diet.

To date, over 7,300 subjects have received FCM in completed clinical studies. The most commonly reported ADRs that have occurred in between 1% and 10% of subjects were headache, dizziness, hypertension, nausea, injection site reactions, flushing and hypophosphataemia. No reported ADRs were very common (≥10%).

Please refer to the Investigator's Brochure for full list and description of risks and precautions.

8.3 Sodium Chloride (NaCl 0.9%)

One mL of NaCl 0.9% solution contains 9 mg (0.39 mmol) of sodium. This has to be taken into account in subjects on a sodium-controlled diet.

9. STUDY PROCEDURES

9.1 Description of Study Assessments

The visit schedule and procedures to be carried out at each visit are shown in the flow chart (see Table 2).

9.2 Schedule of Assessments

For a detailed schedule of assessments (including all protocol required assessments, visits and visit windows) please refer to Table 2.

9.2.1 Screening Procedures

9.2.1.1 Screening Visit

The AHF hospitalisation will be considered as the Index hospitalisation. The screening visit will be performed in-hospital. The following will be done at the screening visit:

- Obtain written informed consent from potentially eligible subjects and complete subject demographics.

  The Investigator will obtain written informed consent from potentially eligible subjects before any trial-related procedure is performed. The informed consent information in addition to the subject demographics will be reported in the eCRF.

- A blood test which will be analysed locally will be performed to determine if the subject is iron deficient and if the Hb ≥8 g/dL* and ≤15 g/dL. The assays to be performed are: serum ferritin, TSAT and Hb. In addition, serum phosphorus levels analysed locally from the same blood draw will be documented in the eCRF.

  *Following section in italics is applicable for The Netherlands, Spain and Singapore only (**NL, ES and SG only**):

  The lower threshold of Hb values is set to 10 g/dL.

- During the same blood draw, a serum pregnancy test will be taken for females of childbearing potential.

- The date when the blood tests were performed will be reported in the eCRF.

- If available in the subject clinical records within the Index hospitalisation, the latest serum creatinine value measured before randomisation will be collected.

- The Investigator will review the main eligibility criteria to determine the potential eligibility of the subject concerned to be randomised in the AFFIRM-AHF trial.

- As of the signing of informed consent for each subject, AEs and changes/additions made to concomitant medications must be documented in the eCRF. Serious adverse events will be reported as they occur but no later than 24 hours after the Investigator's awareness of the event.

9.2.1.2 Baseline Visit, Randomisation and Administration of the First Dose of Study Treatment

The baseline visit will be performed in-hospital for subjects from whom the screening visit blood test results confirm ID and Hb ≥8 g/dL* and ≤15 g/dL. For females of childbearing potential, the serum pregnancy test must be negative.

*Following section in italics is applicable for The Netherlands, Spain and Singapore only (**NL, ES and SG only**):

The lower threshold of Hb values is set to 10 g/dL.

The following assessments will be performed for the baseline visit:

- Completion of the self-administered KCCQ-12 and European quality of life – 5 dimensions questionnaire (EQ-5D) (see Section 9.2.3.10)
- Physical examination (see Section 9.2.3.2)
- Recording of body height and weight (see Section 9.2.3.3)
- Recording of vital signs (i.e. seated blood pressure, pulse rate, and rhythm (see Section 9.2.3.3)
- 12-lead electrocardiogram (ECG) (see Section 9.2.3.7)
- Recording of the appropriate medical history (see Section 9.2.3.1)
- Assessment of symptoms and signs related to HF (see Section 9.2.3.5)
- Assessment of NYHA class (see Section 9.2.3.6)
- Documentation of prior and current concomitant treatments (see Section 9.2.3.8)
- Check for the occurrence of AEs since the signing of informed consent (see Section 10)
- Final review of inclusion/exclusion criteria and confirmation of eligibility (see Sections 5.2 and 5.3)
- Randomisation (see Section 9.2.3.12)

- Blood sampling for biomarkers in a subset of subjects (see Section 9.2.3.11)
- Prepare and administer first dose of study treatment (see Section 9.2.3.13)
- Hand-out subject identification card at hospital discharge
- Provision of the self-administered questionnaire (KCCQ-12) for completion at Telephone Call 1 (Week 2) and Telephone Call 2 (Week 4)

9.2.2 Post-randomisation Visits

9.2.2.1 Outpatient Clinic Visits

All subjects will be followed for a maximum of 52 weeks (after randomisation). During the follow-up phase, subjects will come to the outpatient clinic at Week 6 (Visit 3), Week 12 (Visit 4), Week 24 (Visit 5) and Week 52 (Visit 6) after randomisation.

Note: due to the COVID-19 pandemic situation the Investigator can perform the 52 week visit (Visit 6) via remote methods (such as phone calls, video calls, etc.) to ensure collecting at a minimum subject's health status, AEs and concomitant medications.

The following will be done during the outpatient clinic visits:

- At Week 6 (Visit 3) and Week 52 (Visit 6) only: Collect the self-administered (paper) questionnaires (KCCQ-12 and EQ-5D) completed by the subject at Week 2, Week 4 and at Week 36 respectively
- Completion of the self-administered KCCQ-12 (see Section 9.2.3.10)
- Completion of EQ-5D at Week 6 (Visit 3), Week 24 (Visit 5) and Week 52 (Visit 6) (see Section 9.2.3.10)
- Assessment of symptoms and signs related to HF (see Section 9.2.3.5)
- Assessment of NYHA class (see Section 9.2.3.6)
- Body weight (see Section 9.2.3.3)
- Vital signs (i.e., seated blood pressure, pulse rate and rhythm) (see Section 9.2.3.3)
- Documentation of changes made to/additions of concomitant treatments (see Section 9.2.3.8)
- Blood test to determine if ID persists. The following assays should be performed: serum ferritin, TSAT and Hb. In addition, serum phosphorus levels analysed locally from the same blood draw will be documented in the eCRF (see Section 9.2.3.11).

- Serum pregnancy test (except at Week 52 (Visit 6) for females of childbearing potential (see Section 9.2.3.11)

- Blood test for biomarkers at Week 6 (Visit 3), Week 24 (Visit 5) and Week 52 (Visit 6) in a subset of subjects (see Section 9.2.3.11)

- At Week 6 (Visit 3) only: Administer the repletion dose of study treatment based on the iron need as assessed at the baseline visit. Dosing only in subjects for whom Hb at Week 6 (Visit 3) ≤15 g/dL and if serum pregnancy test is negative in women of childbearing potential (see Section 9.2.3.13)

- At Weeks 12 (Visit 4) and 24 (Visit 5) only: Administer study treatment ONLY if ID persists and Hb ≥8 g/dL* and ≤15 g/dL and serum pregnancy test negative for women of childbearing potential (see Section 9.2.3.13)

*Following section in italics is applicable for The Netherlands, Spain and Singapore only (**NL, ES and SG only**):

The lower threshold of Hb values is set to 10 g/dL.

- Assessment of and reporting of events suggestive of the study outcomes (see Section 9.2.3.14)

- 12-lead ECG at Week 52 (Visit 6) only (see Section 9.2.3.7)

- Physical examination at Week 52 (Visit 6) only (see Section 9.2.3.2)

- Check for the occurrence of AEs. Document the events accordingly (see Section 10)

- At Week 24 (Visit 5) only: Provision of the self-administered questionnaire (KCCQ-12) for completion at Week 36 (Telephone Call 3)

- If ID persists at Week 52 (Visit 6), subjects should be treated in accordance with local routine/standard care

9.2.2.2 Refusal of Subjects to Come to the Outpatient Clinic Visits

If subjects refuse to come in person to the outpatient clinic visit, at the very least, they should be contacted by telephone to ascertain whether they have experienced a deterioration of their disease, if they were hospitalised since the last visit and whether the subject experienced any other AE. In case of a deterioration of the subject's clinical status, the subject will be asked to consult the investigational site personally for further investigations and/or further treatment. The outcome/findings of the telephone call will be documented in the subject's source data and in addition, the required data will be entered in the eCRF. If the subject reports a hospitalisation, the Investigator must verify this information and must report the SAE as per the protocol requirements (see Section 10).

9.2.2.3 Telephone Contact

The site will contact the subject by telephone at Week 2 (Telephone Call 1), Week 4 (Telephone Call 2), and Week 36 (Telephone Call 3), after randomisation to enquire about the subject's health status and enquire if the subjects experienced a deterioration of their condition or if they were hospitalised since the last visit contact and/or if there were changes made to their concomitant treatments. The latter will be reported in the eCRF. The subjects will be requested to complete the KCCQ-12 questionnaire at home on the same day as the Week 2, Week 4 and Week 36 telephone call. The subjects will be instructed to return the completed questionnaires at the following outpatient clinic visit. Adverse events will also be reported in the eCRF. If the subject reports a hospitalisation, the Investigator must report the SAE as per the protocol requirements (see Section 10).

9.2.2.4 Extra Visits

Subjects may be seen at the out-patient clinic for a medical reason related to the AFFIRM-AHF trial outside the scheduled visits defined by the protocol. Data collected during such visits will be recorded on the Unscheduled Visit eCRFs designed for this purpose. If the reason for performing an extra visit constitutes a (serious) AE, this information must be documented as an event (see Section 10).

9.2.2.5 Premature Termination of Follow-up

Subjects who withdraw informed consent for further follow-up prior to Week 52 (Visit 6), should be requested to return to the outpatient clinic as soon as possible after the date when the informed consent was withdrawn. The assessments as shown in Table 2 should be performed and reported in the eCRF.

9.2.3 Clinical and Laboratory Assessments

9.2.3.1 Medical History

A medical history will be taken during the baseline visit. Information to be collected will include the aetiology of HF, the date when HF was first diagnosed, and other clinically relevant past and present medical conditions which were diagnosed/occurred up to at least 12 months prior to signing the informed consent and/or for which the subject is currently treated. Any medically important conditions sustained by the subject which extend beyond 12-months prior to informed consent, should also be reported in the medical history eCRF. If available in the subject clinical records within the Index hospitalisation, the latest serum creatinine value measured before randomisation visit will be collected.

9.2.3.2 General Physical Examination

A routine general physical examination must be performed at the baseline visit and at Week 52 (Visit 6). Any clinically relevant abnormalities or findings must be recorded in the baseline visit section of the eCRF. Any new clinically relevant finding as assessed by the Investigator, must be reported as an AE (see Section 10).

9.2.3.3 Body Height, Weight

Body height (in cm, without shoes) must be measured at the baseline visit only. Body weight must be measured in underwear or light clothing without shoes. The same calibrated scale must be used throughout the trial. Any new clinically relevant change in body weight must be reported as an AE (see Section 10).

9.2.3.4 Vital Signs

The subject's seated systolic and diastolic blood pressure in addition to pulse rate and rhythm must be measured after at least 10 minutes of rest. If blood pressure is measured manually, the diastolic blood pressure must be read at the disappearance of sounds (Korotkoff Phase V). If the disappearance of sound is not detectable, Korotkoff Phase IV should be used for manual measurements; care must be taken not to miss a "silent gap". Any new clinically relevant change as assessed by the Investigator, in blood pressure readings, pulse rhythm or rate must be reported as an AE (see Section 10).

9.2.3.5 Symptoms and Signs of Heart Failure

The Investigator must assess the following HF symptoms:

- Dyspnoea on exertion,
- Dyspnoea at rest while sitting,
- Orthopnoea, and paroxysmal nocturnal dyspnoea.

The Investigator must assess the following clinical signs for HF:

- Peripheral oedema,
- Pulmonary congestion (crackles, rales),
- Liver enlargement,
- Presence of a third heart sound (S_3 gallop),
- Jugular venous distension.

Any new clinically relevant symptom or sign of worsening HF, as assessed by the Investigator, must be reported as an AE (see Section 10).

The HF symptoms and findings which are part of the inclusion criteria must be documented in the Source Data (see Section 5.2).

9.2.3.6 New York Heart Association Functional Classification

NYHA functional classification [34] will be done using the classification as shown Table 3.

Table 3 New York Heart Association Classification

Class	Description
Class I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea, or anginal pain.
Class II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain.
Class III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea, or anginal pain.
Class IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Any new clinically relevant change in the NYHA class as assessed by the Investigator, must be must be reported as an AE (see Section 10).

9.2.3.7 12-lead Electrocardiogram

A 12-lead ECG must be performed at baseline and Week 52 (Visit 6). A scanned image of the ECG will be uploaded in the eCRF.

At baseline, the Investigator must document clinically relevant ECG findings on the appropriate Baseline eCRF pages and in the subject's hospital records. Any new clinically relevant ECG finding or aggravation/worsening of an already existing finding as assessed by the Investigator, must be reported as an AE (see Section 10).

9.2.3.8 Documentation of Concomitant Treatments

All medications and treatments prescribed at the moment of informed consent must be documented on the appropriate eCRF pages. In addition, treatments prescribed up to at least 3 months prior to obtaining the informed consent must be documented on the appropriate eCRF pages, irrespective if the treatment is still ongoing at the time of screening. This includes the recording in the eCRF of all medications/treatments prescribed for the AHF episode.

All changes to or addition of concomitant treatments as of informed consent must be recorded (including changes in dose, change in formulation, starting or stopping medications) in the eCRF. If the indication for changing a subject's concomitant treatment constitutes a new medical condition or a worsening of an existing clinical condition which is considered by the Investigator as being clinically relevant, the indication must be documented as an AE (see Section 10).

9.2.3.9 Final Review of the Inclusion/Exclusion Criteria

Before randomising the subject, the Investigator must ensure that all of the inclusion criteria are present and that none of the exclusion criteria are present.

9.2.3.10 Health-related Quality of Life

KCCQ-12 – Kansas City Cardiomyopathy Questionnaire

Health-related quality of life (HRQoL) will be assessed using the validated KCCQ-12. The KCCQ-12 is a self-administered, disease-specific instrument for measuring HRQoL in subjects with HF regardless of aetiology. It is a 12-item questionnaire that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and QoL [35]. Validated official translations in the local language versions will be used. The subject should complete the paper-based KCCQ-12 before any other assessment or procedure for the visit concerned is performed. The subject should complete the questionnaires in a quiet environment.

Source data verification will be performed for paper-based questionnaires. Once completed by the subjects, data will be entered into the eCRF by site staff. The manual of operations will detail how the data flow will be handled.

EQ-5D – European Quality of Life – 5 Dimensions

The EQ-5D questionnaire is a brief, utility-based generic HRQoL instrument. It consists of a health descriptive system and a visual analogue scale (VAS) for respondents to self-classify and rate their health status on the day of administration of the instrument. [36] The descriptive system has 5 items/dimensions (i.e. mobility, self-care, usual activities, pain/discomfort and anxiety/depression). The VAS is a vertical, graduated (0-100 points) 20 cm “thermometer”, with 100 at the top representing “best imaginable health state” and 0 at the bottom representing “worst imaginable health state”. The VAS records the respondent’s self-rated health on a 20 cm vertical, VAS with endpoints labelled “the best health you can imagine” and “the worst health you can imagine”. This information can be used as a quantitative measure of health as judged by the individual respondents. Validated official translations in the local language versions will be used. The subject should complete the paper-based EQ-5D after the KCCQ-12 but before any other assessment or procedure for the visit concerned is performed. The subject should complete the questionnaires in a quiet environment.

Source data verification will be performed for paper-based questionnaires. Once completed by the subjects, data will be entered into the eCRF by site staff. The manual of operations will detail how the data flow will be handled.

9.2.3.11 Laboratory Tests Mandated by the Study Protocol

The laboratory tests mandated by the trial protocol to be transferred into the eCRF will be analysed locally. The assays to be performed are Hb, serum ferritin, TSAT, serum phosphorus and serum pregnancy tests in females of childbearing potential.

If available in the subject clinical records within the Index hospitalisation, the latest serum creatinine value measured before randomisation visit will be collected.

Iron status blood test reports and serum phosphorus levels received after randomisation must be provided directly to the unblinded Investigator. This person must enter the results in the eCRF page provided for this purpose.

In addition, blood samples for biomarkers will be taken in a subset of subjects. The baseline biomarker blood sample will be drawn just prior to the injection of study treatment. Blood samples will be stored for up to three years after the end of the trial for future analyses of biomarkers of scientific interest. Details concerning the blood samples storage will be provided in an instruction manual and results of these exploratory analyses will be not part of the clinical study report of the main study.

9.2.3.12 Randomisation

Upon completion of the baseline visit procedures/assessments, eligible subjects will be randomised using a validated centralised procedure (IWRS) to either FCM or placebo. Study treatment must be administered on the same day as randomisation. To accommodate local hospital practice, the first dose of study treatment may be administered either on the same day or the day before the planned discharge day. Note that a planned overnight stay following study treatment administration does NOT fulfil the criteria of an SAE unless there is a medical reason for doing this. The randomisation system will allocate the study treatment pack number(s) which should be used for the subject concerned.

9.2.3.13 Administration of Study Treatment

The unblinded Investigator will determine the dose of study treatment to be administered as shown in Table 1. After administration of the first dose of study treatment by the unblinded study personnel, each subject should be observed for adverse effects for at least 30 minutes following each injection of study treatment. Thereafter, at the discretion of the Investigator, subjects may then be discharged from hospital (i.e., following the Index hospitalisation) and for the follow-up visits, may leave the outpatient clinic at the discretion of the Investigator. The complete details concerning the study drug administration procedures will be detailed in the manual of operations.

9.2.3.14 Reporting of Events Suggestive of the Study Outcomes

Reported AEs will be assessed to determine if they are suggestive of the study outcomes – this includes emergency room admissions and unscheduled outpatient clinic visits to treat worsening HF. For such events, the sites will be requested to provide additional information and source documentation (e.g., discharge letters, laboratory/investigational test results) concerning the event which will be used by the CEC to adjudicate the event concerned. All source documentation provided to the CEC will be anonymised.

9.2.4 Treatment Procedures

Details concerning the preparation and administration of study treatment may be found in Section 7.2.2.

9.2.5 Data Which Must be Available in Source Data

9.2.5.1 Laboratory Test Results

The blood test results for assays performed under normal routine and/or during the Index hospitalisation and which determine the subject's eligibility must be available in the source data. The assays concerned are: BNP or NT-proBNP performed ≤72 hours of the AHF admission (i.e., Index hospitalisation), alanine transaminase and aspartate transaminase. The BNP or NT-proBNP value used to determine eligibility will be documented in the eCRF.

Any new clinically relevant changes, as assessed by the Investigator, in laboratory tests performed under normal routine during the follow-up period of the trial must be reported as an AE (see Section 10). The results of the laboratory tests concerned must be available in the source data.

9.2.5.2 Symptoms and Clinical Findings Relating to Heart Failure

The symptoms and signs with which the subject presented at the Index hospitalisation must be documented in the subject's source data.

The date for the LVEF measurement used to determine eligibility must be <12 months prior the randomisation date. The LVEF may have been measured by echocardiography, computerised tomography (CT scan), magnetic resonance imaging (MRI) or ventricular gated single-photon emission computed tomography (SPECT) or radionuclide angiography (MUGA).

9.2.6 End of Treatment Procedures

Not applicable.

9.2.7 End of Study (or Early Discontinuation) Procedures

Upon completion of the study (i.e., at Week 52 (Visit 6)), or if subject is discontinued/withdrawn prior to Week 52 (Visit 6), all assessments should be performed as detailed in Table 2 for such scenarios.

10. EVALUATION, RECORDING AND REPORTING OF AES, SAES AND SPECIAL SITUATIONS

10.1 Definitions

10.1.1 Reference Safety Information

The Reference Safety Information (RSI) presents the basis for expectedness assessment of an adverse reaction for expedited reporting and annual safety reporting, as well as surveillance of subject's safety in a clinical trial by regulatory (and ethic) bodies. In the context of this study, the RSI is contained in Appendix 2 of the Investigator's Brochure.

10.1.2 Adverse Event

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

10.1.3 Adverse Drug Reaction

In the pre-approval clinical experience with a new medical product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered ADRs. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

10.1.4 Unexpected Adverse Event/Adverse Drug Reaction

An AE/ADR, the nature (i.e., specificity/seriousness/outcome/frequency) or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product, or Package Insert/Summary of Product Characteristics for an approved product). Reports which add significant information on the specificity, increase in the rate of occurrence, or severity of a known, already documented serious adverse reaction also constitute unexpected events.

10.1.5 Serious Adverse Event

A SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (the term life-threatening in the definition of serious refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)

- Requires inpatient hospitalisation or prolongation of existing hospitalisation (unless elective surgery (a planned, non-emergency medical procedure))
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (i.e., medically significant)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events should also be considered as serious.

Conversely, some hospitalisations, particularly those which are the result of elective or previously scheduled surgery for pre-existing conditions, treatment on an emergency outpatient basis not resulting in hospital admission or inpatient hospitalisation for social reasons in the absence of any deterioration in the subject's general condition should not automatically be classed as SAEs. Also, a planned overnight stay following study treatment administration does NOT fulfil the criteria of an SAE unless there is a medical reason for doing this.

Any worsening of a pre-existing medical condition or any new medical condition that meets the above SAE criteria should be considered as an SAE.

In case of any worsening of a pre-existing medical condition or any new medical condition occurring that meets the above SAE criteria should be considered as an SAE.

Any suspected transmission of any infectious agent via a medicinal product should be considered as an important medical event (i.e., medically significant) and therefore documented as an SAE.

The Investigator is encouraged to discuss with the Contract Research Organisation (CRO)/Sponsor any AEs for which the issue of seriousness is unclear or questionable.

10.1.6 Suspected Unexpected Serious Adverse Reaction

Any ADR that is both serious and unexpected (per the RSI) that, based on the opinion of the Investigator or Sponsor, is felt to have a reasonable suspected causal relationship to a medicinal product.

Based on the specific study design and the advanced underlying disease state of the recruited subject population, events suggestive of the study outcomes i.e., a re-hospitalisation for an episode of acutely decompensated HF or a CV event leading to death which occurs after discharge for the Index hospitalisation would automatically

qualify to meet the criteria of seriousness in this study. These events would be reported as suspected unexpected serious adverse reactions in cases where there is reasonable suspected causal relationship to a medicinal product.

10.1.7 Special Situations

The following are defined as special situations:

- Use of a medicinal product during pregnancy or breastfeeding
- Medication abuse: the persistent or sporadic, intentional excessive use of study medication
- Medication error: any unintentional error in the prescribing, dispensing or administration of a medicinal product during the study
- Medication misuse: an intentional and inappropriate use of a medicinal product not in accordance with the protocol dose, route of administration, and/or the indication(s)
- Medication overdose: the administration of a quantity of study treatment given per administration or per day which is above the protocol maximum permitted dose
- Occupational exposure: an exposure to a medicinal product for human use as a result of one's professional or non-professional occupation
- Drug interaction
- Unexpected therapeutic or clinical benefit from product use

Suspected adverse reactions associated with medication errors of the investigational medicinal product or use outside that foreseen in the protocol (e.g., overdose or misuse) are also considered as ADRs. Any special situation occurring with/without ADR/AE shall be recorded in the study-specific documentation.

10.2 AE Descriptors

10.2.1 Intensity/Severity Categorisation

The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); however the event itself may be of relatively minor medical significance (such as severe headache). This is not the same as serious, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

In general, the intensity of a particular AE to be recorded is the worst intensity experienced by the subject during the course of the event. The medical assessment of intensity will be determined by using the following definitions:

Mild: The AE is easily tolerated and does not interfere with usual activity.

Moderate: The AE interferes with daily activity, but the subject is still able to function.

Severe: The AE is incapacitating and the subject is unable to work or complete usual activity.

10.2.2 Causal Relationship Categorisation

An Investigator who is qualified in medicine (or dentistry, if appropriate) must make the determination of relationship to investigational product for each AE and SAE. The Investigator should decide whether, in his or her medical judgement, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE/SAE should be classified as unrelated. Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a cause-and-effect relationship between the investigational product and the occurrence of the AE/SAE, then the AE/SAE should be considered certainly, probably/likely, or possibly related. For SAEs, the Investigator must provide a brief comment explaining the rationale of his/her assessment of causal relationship on the SAE form.

The following additional guidance may be helpful:

Term	Relationship	Definition
Certain	Yes	• Event or laboratory test abnormality, with plausible time relationship to study treatment intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	Yes	• Event or laboratory test abnormality, with reasonable time relationship to study treatment intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	Yes	• Event or laboratory test abnormality, with reasonable time relationship to study treatment intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unrelated	No	• Event or laboratory test abnormality which is clearly related to circumstances not connected with the study treatment intake

If the causal relationship between an AE/SAE and the investigational product is determined to be "certainly, probably/likely, or possibly related", the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting. In circumstances where the Investigator has not provided his/her assessment about the relationship, the event will be considered as related and qualify for expedited regulatory reporting.

10.2.3 Outcome Categorisation

Outcome may be classified as: recovered/resolved (i.e., without sequelae); recovered/resolved with sequelae; recovering/resolving; not recovered/not resolved; fatal; or unknown (if follow-up is not possible).

If the outcome of an SAE is reported as recovered/resolved with sequelae, the Investigator should specify the kind of sequelae on the SAE form. If the outcome of an SAE is reported as unknown, the Investigator should specify (on the SAE form) the rationale why unknown was selected.

10.2.4 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the medical history eCRF. A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

10.2.5 Worsening of the Disease Under Study

Symptoms and signs of the disease under study should not be considered AEs as long as they are not regarded as worsening of the clinical features of the disease under study. If a sign or symptom of the disease has unexpectedly worsened in severity or frequency or changed in nature at any time during the study, the symptoms and signs should be recorded as AEs, and clearly marked as worsening of the signs or symptoms in the eCRF.

10.2.6 Clinical Laboratory Evaluations

A change in the value of a safety laboratory investigation can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to a pathological value, or results in a deterioration of Common Terminology Criteria grade, or a further worsening of an already pathological value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are pathological laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a laboratory parameter is clinically significant and therefore represents an AE. If the Investigator considers such an AE as serious (e.g., medically significant event fulfilling criteria per Section 10.1.5), it must be reported as an SAE.

If a laboratory abnormality meeting the above criteria is a sign of a disease or syndrome only the diagnosis should be recorded in the eCRF.

If a laboratory abnormality meeting the above criteria is not a sign of a disease or syndrome, the abnormality itself should be recorded in the eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., “elevated potassium” as opposed to “abnormal potassium”).

If the laboratory abnormality can be characterised by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, hyperkalaemia or hypoglycaemia. Observations of the same laboratory abnormality from visit to visit should not be repeatedly recorded in the eCRF, unless the aetiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

At the end of the study period, all pathological laboratory findings/values diagnosed throughout the treatment period should be reviewed by the Investigator to provide a final clinical assessment in view of the dynamic of laboratory changes/abnormalities.

10.2.7 Abnormal Vital Signs

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the Investigator’s judgment

It is the Investigator’s responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded in the eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded in the eCRF, unless the aetiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

10.2.8 Special Situations

All special situations (see Section 10.1.7) such as study treatment overdose and medication errors including injection rate errors have to be documented in the subject's eCRF (investigational medicinal product accountability and special situations pages as appropriate) and source documents. All special situations, e.g., overdose, or medication errors have to be reported per standard guidelines.

10.3 Reporting Procedure for AEs, SAEs and Pregnancy

10.3.1 Adverse Events

All AEs either observed by the Investigator or one of his/her medical collaborators, or reported by the subject spontaneously, or in response to a direct question, will be noted in the AE section of the subject's eCRF and source documentation. This applies to all AEs regardless of presumed relationship to the study. AEs leading to discontinuation of study treatment should also be collected.

If any AE is reported, the date of onset, relationship to study treatment, any action taken, date of resolution (or the fact that it is still continuing or has become chronic), outcome, intensity (worst at any point during the event) and whether the AE was serious or not at any time during the event will be recorded. In order to establish the duration of any SAE, the dates of hospitalisation and discharge or dates of meeting other SAE criteria will be recorded in the eCRF.

Where possible, the Investigator should report a diagnosis rather than individual signs and symptoms or abnormal laboratory values. However, if a constellation of signs and/or symptoms cannot be medically characterised as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

The Investigator should use standard medical terminology/concepts; avoid colloquialisms and abbreviations. Only 1 AE term should be recorded in each event field in the eCRF.

The AE reporting period begins at the time the ICF is signed by the subject. The AE reporting period ends at the last study/follow-up visit (Week 52 – Visit 6).

AEs that extend continuously, without resolution, between trial assessments should only be recorded once in the eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens.

AEs that resolve and subsequently recur should have each recurrence recorded separately in the eCRF.

All AEs persisting at the time of study completion will be followed by the Investigator through contact with the subject until resolution or stabilisation, or the subject is lost to follow-up and cannot be contacted. The outcome must be documented in the subject's source documents.

If the subject reports an AE, it is the Investigator's responsibility to acquire sufficient information in order to assess causality. This may require additional laboratory testing, physical examinations, telephone contacts, etc.

In order to avoid bias in eliciting AEs, subjects should be asked a non-leading question, such as "How are you feeling?" It is also important to question the subject in a non-leading way about changes in their health or concomitant medication usage since their last visit. This information should be collected prior to completion of assessments at all study visits. In addition, any symptoms/conditions reported during assessments and deemed to be clinically significant by the Investigator will be assessed as AEs.

10.3.2 Serious Adverse Events

The occurrence of an SAE must be immediately reported to Vifor Pharma (or its delegate; e.g., CRO) within 24 hours of awareness. This includes all SAEs (independent of relationship to study treatment) occurring from the time the informed consent is signed until 30 days following the last study visit or until 30 days after last study drug administration, whichever is longer. The final follow-up may be conducted as a telephone call rather than a formal visit, but the Investigator must report any SAEs that occur during this period. SAEs starting before first administration of study treatment must be identified as such.

A death occurring during the study or which comes to the attention of the Investigator within 30 days after the last study visit or until 30 days after the last study treatment administration, whichever is longer, whether considered treatment-related or not, must be reported to the CRO/Vifor Pharma.

SAEs must be reported by entering the SAE information into the eCRF. CRO (Worldwide Clinical Trial Pharmacovigilance department) will receive notification of the initial SAE via an email alert generated from the electronic data capture system.

The electronic SAE form will be completed with the following information at a minimum:

- Event description/verbatim (including onset date of the SAE, outcome and reason for it being considered serious)
- Relationship to investigational product (i.e., causality)
- Name of the investigational product (including study treatment dose and administration dates)
- Action taken with the investigational product
- Severity of the event

Additional information must be uploaded to the eCRF when available including any relevant records (e.g., hospital discharge summary, autopsy report/death certificate, etc.). Any supporting information provided should not reveal a subject's identity beyond the agreed study identifier. The Investigator should ensure that information reported is accurate and consistent.

If the Investigator is unable to access the eCRF, the report may be done by facsimile or email using the study-specific Vifor Pharma SAE form provided by Vifor Pharma (see Appendix 1). The Investigator must complete, sign and date the SAE pages, and verify the accuracy of the information recorded on the SAE pages with the source documents. The Vifor Pharma SAE form must be completed in capital letters, in medical terms, in English and to the best extent possible given the time constraints. Any supporting documentation should be sent along with the Vifor Pharma SAE form.

At a minimum the following should be provided at the time of the initial SAE report:

- Study name and/or number
- Subject number, age and sex
- Event description/verbatim (including onset date of the SAE, outcome and reason for it being considered serious)
- Relationship to investigational product (i.e., causality)
- Name of the investigational product (including study treatment dose and administration dates)
- Action taken with the investigational product
- Severity of the event

- Investigator name and address
- Name of the reporter (including site name or number and country), and
- Dated signature of the Investigator or Sub-/Co-Investigator

A safety contact sheet will be provided by the Sponsor to the Investigator (prior to first subject providing informed consent) detailing all applicable contact information. This will be kept up to date with any changes being provided to the Investigator immediately.

Pharmacovigilance Department
Worldwide Clinical Trials
Fax: [redacted]
Email address: [redacted]

The SAE information must be entered onto the SAE eCRF as soon as the web-based system becomes accessible.

Follow-up information must be handled in the same way and reported within the same time frame as the initial report.

Where possible, the Investigator should report a diagnosis rather than signs and symptoms.

Death should be considered an outcome and not a distinct event. In case of a fatal outcome, the Investigator should provide a working diagnosis (event which caused outcome, e.g., death due to fatal myocardial infarction) instead of reporting only death; and an autopsy report should be provided where possible. If the cause of death later becomes available (e.g., after autopsy), this working diagnosis should be replaced by the established cause of death.

The onset date of the SAE is defined as the date the signs and symptoms/diagnosis became serious, i.e., met at least 1 of the International Council for Harmonisation (ICH) criteria for seriousness. The resolution date of the SAE is defined as when the symptoms resolve, or the event is considered chronic (e.g., sequelae) or stable, and/or if the seriousness criteria are no longer applicable. SAEs that are ongoing at the time of death are considered unresolved.

All recorded SAEs, regardless of relationship to investigational product, will be followed up until resolution, stabilisation, or the subject is lost to follow-up and cannot be contacted. No further updates should be entered into the eCRF after the completion of the final safety follow-up period, but should be notified to the CRO/Vifor Pharma using the Vifor Pharma SAE form. In circumstances where the Investigator is unable to make contact with the subject (or his/her relatives), the Investigator must provide a written statement (recorded in the subject's source documents) to the CRO/Vifor Pharma, confirming that the subject is lost to follow-up.

Vifor Pharma, or its delegate, is responsible for expedited reporting to the relevant Regulatory Authorities, to Investigators and to local and central Institutional Review Board/Ethics Committee/Independent Ethics Committee (IRB/EC/IEC) as per local regulations.

Any SAE considered to have a causal relationship (i.e., related) to the investigational product and discovered by the Investigator at any time after the study should be reported. A rationale for the assessment of a causal relationship must be provided by the Investigator. Any safety information that is obtained after database lock of the clinical database will be documented in the safety database and implications for handling the data in the clinical database assessed on an individual case basis.

Additional detail regarding SAE reporting procedures and management is available in the study-specific SAE Processing and Reporting Plan, which will be provided in the study documentation.

10.3.2.1 Elective Surgery/Routine Examination

Elective surgery (a planned, non-emergency medical procedure) and in-patient routine examination for a pre-existing condition (i.e., recorded in the medical history) do not qualify as SAEs as long as the procedure was not performed as a result of a worsening of the condition. However, AEs which occur during any elective hospitalisation will need to be collected and reported.

10.3.3 Pregnancy

When a female subject becomes pregnant during the study and study treatment has been administered to the subject, the outcome of the pregnancy needs to be monitored and the safety of the mother and unborn child need to be safeguarded (as per protocol, pregnancy is an exclusion criteria). Therefore, the outcome of all such pregnancies (including normal births) must be followed up and documented, even if the subject was withdrawn from the study or the study has been completed.

Women of childbearing potential should have a negative serum pregnancy test prior to randomisation. Study treatment should not be initiated by the Investigator until a report of a negative pregnancy test has been obtained.

A highly effective contraception must be used in female subjects of childbearing potential before beginning study treatment, during study dosing, and for 30 days following discontinuation of study treatment.

Following sections in italics are applicable for United Kingdom only (**UK only**):

Highly effective birth control methods include:

- *Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation*

  - *Oral*
  - *Intravaginal*
  - *Transdermal*
- *Progestogen-only hormonal contraception associated with inhibition of ovulation*
  - *Oral*
  - *Injectable*
  - *Implantable*
- *Intrauterine device*
- *Intrauterine hormone-releasing system*
- *Bilateral tubal occlusion*
- *Vasectomised partner*
- *Sexual abstinence*

Due to the follow-up of 52 weeks per patient after randomisation in the present study, sexual abstinence is only acceptable as 'true abstinence' when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of contraception.

A female subject must immediately inform the Investigator if she becomes pregnant during the study and no further study treatment shall be administered. The Medical Monitor must be contacted immediately to break the blind (if applicable). The Investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

The Investigator/Sponsor is responsible for monitoring the subject and pregnancy outcome. Every effort should be made to gather information regarding the pregnancy outcome until 90 days postpartum (or otherwise as appropriate). It will be the responsibility of the Sponsor, together with the appropriate support of the Investigator, to obtain this information.

Any report of pregnancy recorded for any female subject should be reported to the CRO/Vifor Pharma within the same timelines as a SAE, i.e., immediately (within 24 hours of awareness). The Investigator should complete a Vifor Pharma Report on Exposure to Medicines During Pregnancy form (see Appendix 2) and forward to the CRO/Vifor Pharma. Complications of pregnancy such as abortion (spontaneous or

induced), premature birth (before 37 weeks gestational age) or congenital abnormality are considered SAEs and should be reported using the study-specific Vifor Pharma SAE form.

All pregnancies occurring in a female subject within 90 days after discontinuation of investigational product should be reported within the same timelines as a SAE to the CRO/Vifor Pharma.

11. STUDY COMMITTEES

11.1 DSMB/DMC Procedures

A DSMB/DMC will be constituted to protect the safety of study participants. A DSMB/DMC is a group of independent experts external to a study assessing the progress, safety data and, if needed critical efficacy endpoints of a clinical study. Most DSMBs/DMCs are composed of clinicians with expertise in relevant clinical specialties and at least 1 biostatistician knowledgeable about statistical methods for clinical trials and sequential analysis of trial data. For trials with unusually high risks or with broad public health implications, the DSMB/DMC may include a medical ethicist knowledgeable about the design, conduct, and interpretation of clinical trials. For practical reasons the number of members of a DSMB/DMC should be limited.

The DSMB/DMC will receive blinded eCRF data in the form of tables and listings (prepared by an independent statistician), and adjudicate on subject status changes and dosing decisions (where appropriate). Where appropriate, the DSMB/DMC may receive unblinded data (on a subject level or treatment group level) that should be reviewed in a closed session. The data should include, but is not limited to, demographics, subject enrolment, baseline characteristics, AE data, SAE data (by severity and causality), laboratory data, dose adjustments, protocol adherence, and subject withdrawals. The DSMB/DMC will evaluate the progress of the trial, assess data quality and timeliness, participant recruitment, accrual and retention, and participant benefit/risk. In addition the DSMB/DMC will monitor external factors relevant to the trial, for example scientific and therapeutic developments that may affect participant safety or ethical status. Based on the observed benefits or adverse effects, the DSMB/DMC will make recommendations to the Sponsor concerning continuation, termination or modifications of the trial.

The Sponsor will establish a charter document explaining the working procedures and responsibilities of the DSMB/DMC. The charter should be agreed to by the DSMB/DMC.

11.2 Steering Committee

The Steering Committee (SC), chaired by Co-ordinating Investigator, will be responsible for maintaining the scientific integrity of the trial. Members will be selected investigators from the participating countries/regions. The Co-ordinating Investigator will review and approve the trial protocol and subsequent protocol amendments, taking into account also feedback from other SC members, if applicable. The SC will be blinded to study treatment allocation while the trial is ongoing. Each SC member is expected to discuss with the SC Chairman any activities that might constitute a conflict of interest for the AFFIRM-AHF trial.

SC meetings will be attended by, in addition, representatives of the Sponsor and coordinating personnel (if applicable), in a non-voting capacity.

11.3 Clinical Endpoint Committee

An independent CEC will be formed to adjudicate all events suggestive of the study endpoints using prospectively defined criteria which will be detailed in the CEC charter. Members of the CEC will not be employees of Sponsor. This committee will be composed of at least three members including at least one cardiologist specialising in HF. The CEC will adjudicate the events blinded to study treatment group allocation. Endpoint adjudication will be done, using a web-based adjudication system, on an ongoing basis throughout the duration of the trial. The adjudicated events will be used for the analyses of the primary endpoint, secondary and other endpoints.

12. STATISTICAL ANALYSIS

12.1 Statistical Methods

All statistical analyses will be performed using SAS Version 9.3 or later (SAS Institute Inc. SAS/STAT, Cary, NC, United States). The level of significance to be used will be 0.05. Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be finalised prior to unlocking of the study data base. A general description of the planned methods is provided below. Any deviation from the SAP will be noted and explained in the final study report.

12.2 Sample Size and Power Calculations

The recurrent HF hospitalisation and CV death rates in the control group was extrapolated as 0.9 events/year using the data from the EVEREST study [37] and as 0.61 events/year using the data from the ESC-HF study [38]. For this study, it is anticipated that approximately 35% of subjects will sustain either a CV death or will sustain at least one HF hospitalisation. It is also anticipated that 12% of subjects will sustain a CV death. Assuming that 50% of subjects who sustain a CV death will not undergo any prior HF hospitalisation and that the average number of HF hospitalisations per subject with at least one HF hospitalisation will be estimated as 2, the number of events per 100 years has been estimated as follows: 12 CV deaths + 2*(35-6) HF hospitalisations, which equates to approximately 70 events/100 years of follow-up for HF hospitalisations and CV death.

Concerning the event rate ratio, it is assumed that there will be a 30% reduction in HF hospitalisations for subjects allocated to FCM and that CV death rates will be similar between the FCM and placebo groups. It is therefore assumed that the rate ratio between FCM and placebo for the composite of recurrent HF hospitalisations and CV deaths will be approximately 25%.

The dispersion factor used in negative binomial regression is a measure of the mean-variance. There is currently insufficient data to estimate the negative binomial dispersion. For this sample size calculation, a dispersion factor (K) of 1 was assumed.

The sample size calculation was done in the software NCSS PASS-14 [39] using the sample size formula proposed by Zhu and Lakkis 2014 [40] to compare two negative binomial rates.

Assuming a recurrent HF hospitalisation and CV death of 0.7 events/year the placebo group, in total, 1,000 subjects (500 per study treatment group) would be required to demonstrate a statistically significant rate ratio of 0.75 (i.e., 25% reduction of recurrent events between the FCM and placebo groups) with a power of 80% and a 2-sided alpha of 0.05. Taking into account 9% loss to follow-up, a sample size of 1,100 subjects (550 per treatment group) is planned.

12.3 Analysis Sets

12.3.1 Full Analysis Set

The full analysis set (FAS) will consist of all subjects who satisfy the following criteria:

- Randomised to either of the two treatment groups
- The administration of study treatment was started

The FAS data set will be analysed based on the randomised treatment arm.

12.3.2 Per-protocol Set

The per-protocol (PP) analysis set will consist of all subjects who, in addition to the FAS criteria, had no major protocol violations (as defined in the SAP).

12.3.3 Safety Set

The safety set will consist of all randomised subjects administered at least 1 dose of study treatment. The subjects in this group will be analysed based on the treatment received.

12.4 Background and Demographic Characteristics

The baseline and demographic characteristics will be summarised per treatment group.

12.5 Study Treatment

The total amount of study treatment given will be calculated for each subject and will be compared to the amount expected to be given for each subject. Treatment compliance will be calculated for each subject and summarised by treatment group.

12.6 Concomitant Therapy

Concomitant medications will be categorised according to a standard dictionary (World Health Organization Drug Classification). Counts and percentages of subject use for each medication will be computed and summarised by treatment group.

12.7 Efficacy Evaluations

12.7.1 Primary

The primary outcome is the composite of recurrent HF hospitalisations and CV death up to 52 weeks after randomisation.

The HF hospitalisation and CV death rates per 100 patient-years of follow-up as adjudicated by the CEC, will be calculated by dividing the total number of HF hospitalisations, and CV deaths by the total follow-up duration of all subjects in each group. The rate ratio (95% CI and p-value) for this analysis will be analysed using a negative binomial model. Compared to the Poisson distribution, the negative binomial

distribution allows for different individual tendencies (frailties) with respect to their risks of repeat hospitalisations [41].

The negative binomial model will be adjusted for the following baseline covariates: sex, age, HF aetiology (ischemic/non-ischemic), HF duration (newly diagnosed at Index hospitalisation/known documented HF prior to Index hospitalisation) and country. A sensitivity analyses will be performed using an unadjusted model.

The primary outcome analysis will be performed on the FAS will use the CEC adjudicated events. A sensitivity analysis will be performed on the PP population set.

Descriptive statistics will provide, per treatment group, the total number of events and the number (%) of subjects with at least one event.

A graphical representation of the estimated cumulative hazard rate will also be provided.

As the analysis of HF hospitalisations could be confounded by the competing risk of death, a confirmatory analysis will be performed on the FAS population set using the joint frailty model in order to analyse repeat hospitalisation rate whilst accounting for their associated mortality rate [42].

12.7.2 Secondary and Other Endpoints

The secondary endpoints will evaluate, relative to placebo, the effect of IV FCM.

Hochberg's procedure will be used to control the overall Type I error for the evaluation of the secondary endpoints. The secondary endpoints are the following:

- The composite of recurrent CV hospitalisations and CV death up to 52 weeks after randomisation.
- HF hospitalisations up to 52 weeks after randomisation (analysed as recurrent event).
- CV mortality analysed as time to first event at 52 weeks after randomisation.
- The composite of HF hospitalisations or CV death analysed as time to first event at 52 weeks after randomisation.
- Days lost due to HF hospitalisations or CV death at 52 weeks after randomisation.

Complete details concerning the analyses of the secondary endpoints and the statistical tests to be performed will be detailed in the SAP – the latter will be finalised prior to unblinding of the trial database.

The other endpoints will evaluate, relative to placebo, the effect of IV FCM on:

- The composite of recurrent HF hospitalisations and CV death up to 30 days after randomisation.
- The composite of recurrent CV hospitalisations and CV death up to 30 days after randomisation.
- The composite of HF hospitalisations or CV death analysed as time to first event at 30 days after randomisation.
- The composite of CV hospitalisations or CV death analysed as time to first event at 30 days after randomisation.
- HF hospitalisations up to 30 days after randomisation (analysed as recurrent event).
- HF hospitalisations up to 30 days and 52 weeks after randomisation (analysed as time to first event).
- CV hospitalisations up to 30 days and 52 weeks after randomisation (analysed as recurrent event and time to first event).
- The composite of CV hospitalisations or CV death analysed as time to first event at 30 days and 52 weeks after randomisation.
- Cardiovascular mortality analysed as time to first event at 30 days after randomisation.
- All-cause mortality analysed as time to first event at 30 days and 52 weeks after randomisation.
- Proportion of patients with an event (HF hospitalisations, CV hospitalisations, CV mortality, composite and individual categories).
- Change from baseline in NYHA functional class as assessed at 6, 12, 24 and 52 weeks after randomisation.
- Change from baseline in the Kansas City Cardiomyopathy Questionnaire-12 up to 52 weeks after randomisation.
- Change from baseline in the European quality of life – 5 dimensions questionnaire up to 52 weeks after randomisation.
- Days lost due to HF hospitalisations or CV death at 30 days after randomisation.

The analyses of secondary and other endpoints will be performed on the FAS and will use the CEC adjudicated events for hospitalisations and mortality-related outcomes.

For the recurrent event analysis, the same analysis as that described for the primary outcome will be performed.

For the time to first event analysis, the incidence of events will be documented by treatment group with the total number of events, the number of subjects with at least 1 event and the event hazard rate per 100 patient years "at risk" (estimated as the number of patients with at least 1 event divided by the patient years at risk of event). Patient years at risk of event will be taken as the sum of the observation time from start of study treatment until the first occurrence of the event concerned, or until censoring. The hazard ratio (relative to placebo), its 95% CI and the p-value test will be provided using Cox regression. The proportion of patients with an event (HF hospitalisations, CV hospitalisations, CV mortality; composite and individual categories) will also be reported.

The change in NYHA class will be analysed using a repeated measurement analysis of the ordered polytomous regression adjusted for treatment, time and the baseline NYHA value.

Complete details concerning the analyses of the other endpoints and the statistical tests to be performed will be detailed in the SAP – the latter will be finalised prior to unblinding of the trial database.

12.8 Safety Evaluations

The safety analysis will be performed on the Safety analysis set. The following safety outcomes will be analysed:

- Clinical laboratory panels (iron status, serum phosphorus and cardiac biomarkers)
- Summary of AEs: by system organ class (SOC) and preferred term (PT) (Medical Dictionary for Regulatory Activities (MedDRA) coded term), by severity and relation to study product
- Summary of SAEs: by SOC and PT (MedDRA coded term), by severity and relation to study product

All data will be presented in a descriptive manner by providing mean tables (continuous variables) or frequency tables (discrete variables and AEs). Laboratory data will also be presented by shift tables.

For AEs, the total number of events and number (%) of subjects with event will be presented by MedDRA SOC and PT by treatment group.

Complete details concerning the analyses and statistical tests to be performed will be detailed in the SAP.

12.9 Interim Analyses

No interim analyses are planned.

12.10 Other Evaluations

12.10.1 Exploratory Analyses

Additional exploratory analyses not described above may be performed if indicated in the medical review(s) of the data. Such analyses may include subgroup analyses based on various baseline characteristics such as Hb, HF aetiology, duration of HF, baseline serum creatinine and will be fully described in the final SAP.

12.10.2 Biomarker Blood Samples

It is planned to perform biomarker analyses in blood samples from approximately 60% of randomised subjects. The decision concerning which biomarkers will be analysed will be made by in collaboration with the SC, together with the Sponsor. If the biomarker samples will not be analysed, they will be destroyed. Details concerning the blood samples storage will be provided in an instruction manual. The statistical analysis for the biomarker blood samples will be detailed in a separate biomarker SAP and results of these exploratory analyses will be not part of the clinical study report of the main study.

12.10.3 Quality of Life

Quality of Life will be assessed using the KCCQ-12 and EQ-5D. The analysis of treatment difference on the KCCQ-12 score at Week 2, Week 4, Week 6, Week 12, Week 24, Week 36 and Week 52 will be done by comparing the model adjusted means of the corresponding visit based on a model for repeated-measures including terms for treatment, baseline, time and treatment-by-time with an unstructured covariance matrix to model the within-patient variability. The analysis of treatment difference on the EQ-5D score will be done in the same manner for the data collected at Week 6, Week 24 and Week 52. The SAP will detail the analysis to be performed.

12.10.4 Pooling of AFFIRM-AHF, FAIR-HF2 and FAIR-HFpEF studies

Since February 2017, a study (FAIR-HF2: ClinicalTrials.gov Identifier: NCT03036462) is running as multinational trial. The purpose of this study is to determine whether IV iron supplementation using FCM reduces hospitalisation and mortality in patients with ID and HF.

Since August 2017, a study (FAIR-HFpEF: ClinicalTrials.gov Identifier: NCT03074591) is running in Germany. The purpose of this study is to determine whether treatment with IV iron for patients with HF with preserved ejection fraction and ID, both with or without anaemia, can improve exercise capacity as measured by 6-minute walking test and symptoms while being safe.

As there are a lot of similarities between AFFIRM-AHF, FAIR-HF2 and FAIR-HFpEF studies, it has been decided to perform 2 integrated analyses of the 3 studies:

- Integrated analysis 1: AFFIRM-HF and FAIR-HF2 studies

- Integrated analysis 2: AFFIRM-HF, FAIR-HF2 and FAIR-HFpEF studies

For the Integrated analysis 1, the pooling of both databases (AFFIRM-HF and FAIR-HF2) will occur after the database lock of the second incoming study, currently projected to be FAIR-HF2. A specific integrated SAP will be written prior to the database lock of the first incoming study, currently projected to be AFFIRM-AHF. The methods for the Integrated data analysis 1 will be listed and detailed in an integrated SAP and the results reported in an integrated Clinical Study Report separate to the study report of each individual study.

For the Integrated analysis 2, the pooling of the 3 databases (AFFIRM-HF, FAIR-HF2 and FAIR-HFpEF) will occur after the database lock of the last incoming study, currently projected to be FAIR-HFpEF. A specific integrated SAP will be written prior to the database lock of the first incoming study, currently projected to be AFFIRM-AHF. The methods for the Integrated data analysis 2 will be listed and detailed in an integrated SAP and the results reported in an integrated Clinical Study Report separate to the study report of each individual study.

13. STUDY ETHICAL CONSIDERATIONS

13.1 Ethical Conduct of the Study

The study will be conducted according to the principles of the World Medical Association's (WMA) Declaration of Helsinki (as amended by the 64th WMA General Assembly, Fortaleza, October 2013) [43], and the ICH guidelines for GCP [44]. Vifor Pharma will ensure that the study complies with all local, federal or country regulatory requirements.

The Investigator must ensure the anonymity of all subjects participating in the study. Each subject will be assigned a unique subject number and this should be used on all forms associated with the subject's documents or samples that will be supplied to the Sponsor or any party completing testing on behalf of the Sponsor (e.g., blood for central laboratory assessments).

All anonymous data remains the property of Vifor Pharma.

13.2 Informed Consent

The ICF used for the study must comply with the Declaration of Helsinki, federal regulations, and ICH guidelines; and must have been approved by the appropriate IRB/EC/IEC prior to use. The Investigator or an authorised associate must explain orally and in writing the nature of the study and the treatment in such a manner that the subject is aware of potential benefits and risks. Subjects must also be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects must be provided sufficient time to consider participation, including discussion with family members prior to signing the ICF. Documentation of the discussion and the date of informed consent must be recorded in the source documentation. Subjects must give informed consent in writing.

A guideline on how to administer informed consent is attached in Appendix 3 and should be followed by all site staff administering informed consent to subjects when an equivalent process is not available at the site.

13.3 Institutional Review Board or EC/IEC

The protocol, any protocol amendments and consent form for the proposed clinical study and any other documents required by the local IRB/EC/IEC must be submitted by the Investigator for review and approval to the IRB/EC/IEC. The Investigator must also ensure that the IRB/EC/IEC reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study on an annual basis. A copy of the approval letter must be forwarded to Vifor Pharma before the study is implemented.

14. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator must ensure that all trial related site source data, study related documents and reports will be available, and that the provision of direct access for monitoring and auditing by Vifor Pharma or its designees will be permitted. In addition, the Investigator must ensure that all trial related site source data, study related documents and reports will be made available for inspection by the appropriate Regulatory Authority and review by the IRB/EC/IEC.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the Monitor (source document verification), and the maintenance of a study treatment dispensing log by the Investigator. The data collected will be entered (electronic data capture) into the study database and will be verified by the Monitor. A comprehensive validation check program will verify the data and queries will be generated for resolution by the Investigator. Throughout the study, Vifor Pharma or its designates may review data as deemed necessary.

15. ADMINISTRATIVE PROCEDURES

15.1 Sponsor's Responsibilities

15.1.1 Study Supplies

Sites will be provisioned with supplies required to manage this study. This will include but not be limited to:

- Investigator file(s) (for filing of all study related documentation)
- Contact list of all relevant study personnel
- Access to eCRF and completion guidelines
- Study reference manual
- All study forms (e.g., SAE, pregnancy, drug accountability, etc.)

15.1.2 Insurance

Vifor Pharma confirms that it carries liability insurance which protects non-employee physicians or Investigators against claims for which they may become liable as a result of damages caused by Vifor Pharma products used in clinical studies. Insurance coverage is not extended to damages that the Investigators or third parties may suffer by reason of acts of commission or omission on the part of such Investigators or third parties and that are not in accordance with accepted common medical practices (lege artis procedures). Vifor Pharma will reimburse the subject for all study-related injuries provided that the injury does not arise from the subject's misuse of the study treatment or failure to follow the Investigator's instructions.

15.1.3 Investigator Training

All Investigators and their study personnel will receive training regarding the study procedures and GCP/regulations specific to the conduct of clinical trials. This training will take place prior to enrolment of the first subject at the study centre.

15.1.4 Study Monitoring

The study will be monitored by representatives of Vifor Pharma (or designee) who may include a CRO and/or partner company.

It is understood that the responsible Vifor Pharma Monitor (or designee) will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the trial (eCRFs and other pertinent data) provided that subject confidentiality is maintained in accordance with local requirements.

It will be the Monitor's responsibility to inspect the eCRFs at frequent regular intervals throughout the study, to verify adherence to the protocol and the completeness,

consistency and accuracy of the data being entered on them. The Monitor must have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The Investigator (or his/her deputy) agrees to co-operate with the Monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

15.1.5 Medical Monitoring

Vifor Pharma (or designee) will provide a medical contact for the discussion of medical concerns or queries throughout this clinical study. Details of how to access the Medical Monitor will be provided and stored in the Investigator Site File.

15.2 Investigator's Responsibilities

15.2.1 Reporting and Recording of Data

All required study data must be entered in the eCRF created for the study. Training on the system will be provided to all sites, including instructions on how to address missing data, corrections, query procedures and electronic signatures. Only individuals who are identified on the authorised signature page may enter/correct data in the eCRF. For those subjects who withdraw before completion of the study, all available efficacy and safety data must be entered in the eCRF. Incomplete or inconsistent data on the eCRF will result in data queries addressed to the Investigator for resolution.

15.2.2 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which case reports for each subject are based. They are to be separate and distinct from eCRFs. These records should include detailed notes on:

- The medical history up to at least 12 months prior to participation in the study
- The basic identifying information, such as demographics, that link the subject's source documents with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided and any other data on the condition of the subject
- The subject's exposure to study treatment
- All AEs, and pregnancies
- All special situations as defined in Section 10.1.7
- The subject's exposure to any concomitant therapy (including date and quantity dispensed)
- All relevant observations and data on the condition of the subject throughout the study

- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). The date of informed consent must be recorded in the source documentation.

All data for the study must be available in source documentation.

15.2.3 Records Retention

The Investigator must arrange for the retention of all study documentation (eCRF files or printed forms, research files, and master files) for the duration specified in their respective site contract or as specified by the applicable Regulatory Authority, whichever is longer. The Sponsor will inform the Investigator in writing when files can be destroyed. Archived data may be held on microfiche or electronic record, provided that a backup copy exists and that a hard copy can be generated if required.

The Investigator must inform Vifor Pharma immediately if any documents are lost, to be transferred to a different facility, or to be transferred to a different owner.

15.2.4 Site Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

16. PROCEDURE FOR MODIFICATION OF PROTOCOL OR PREMATURE TERMINATION OF THE STUDY

16.1 Protocol Waivers, Deviations and Violations

Protocol waivers shall not be permitted except where necessary to eliminate an immediate hazard to subjects.

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as minor or major on a case-by-case basis. The criteria describing the deviation(s) and how they will be handled will be documented in the SAP.

16.2 Protocol Amendments

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of Vifor Pharma. Each applicable Regulatory Authority/IRB/EC/IEC will review and approve amendments prior to their implementation. Regulatory Authority/IRB/EC/IEC approval need not be obtained prior to removal of an immediate hazard to subjects.

16.3 Study Termination

Vifor Pharma reserves the right to terminate the study in its entirety or at a site at any time. Reasons for termination may include (but are not limited to) unsatisfactory subject enrolment with respect to quality and/or quantity, site is unable to comply with the requirements of the protocol or GCP, or data recording is inaccurate and/or incomplete.

Following sections in italics are applicable for The Netherlands only (**NL only**):

The right by the Sponsor to the terminate the study is only applicable in case certain circumstances are applicable as follows:

a) *If the judgement of the competent medical research ethics committee that has assessed the study is irrevocably revoked*

b) *If a reasonable case can be made for terminating the study in the interests of the health of the research subjects*

c) *If it transpires that continuation of the study cannot serve any scientific purpose, and this is confirmed by the medical research ethics committee that has issued a positive decision on the study*

d) *If one of the parties or the funder has been declared insolvent or a bankruptcy/winding-up petition has been filed in respect of one of the parties or the financier, or one of the parties or the financier is dissolved as a legal entity*

e) *If circumstances beyond the control of the Sponsor, Investigator or funder make it unreasonable to require the study's continuation*

In terminating the study, Vifor Pharma and the Investigator will assure that adequate consideration is given to the protection of the subject's interests. Both parties will arrange the procedures on an individual basis after review and consultation and in accordance with the study contract.

17. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

Vifor Pharma is committed to the timely communication of data from clinical research trials, following the Pharmaceutical Research and Manufacturers of America principles [45]. Where possible, authorship will be agreed at the beginning of the study. The authors will form a publication committee and this committee will propose and develop appropriate scientific manuscripts or abstracts from the study data. Investigators may not present or publish partial or complete study results individually.

Following section in italics is applicable for The Netherlands only (NL only):

In The Netherlands the previous sentence is extended with:

[…]individually, in the initial 12 months after the study's termination prior research results have been disclosed.

Any manuscript or abstract proposed by the Investigators must be reviewed and approved in writing by Vifor Pharma before submission for publication. Names of all Investigators actively participating in the study will be included in the publication.

The publication committee for a study will comprise of authors selected in adherence with the International Committee of Medical Journal Editors criteria [46] for authorship. That is, all authors must meet each of the following 3 criteria:

1. Substantial contribution to conception and design or acquisition of data, or analysis and interpretation of data

2. Drafted the article or revised it critically for important intellectual content

3. Approved the final version for publication

Members of the study SC generally fulfil the authorship criteria through their involvement in protocol design and review, monitoring of and sometimes direct involvement with recruitment, and thus they will usually be part of the publication committee. If studies are multicentre, it may be appropriate to assign group authorship.

In addition, certain Vifor Pharma employees involved in the design and conception of the protocol, study management and data analysis and interpretation are qualified authors and will be included in the publication committee e.g., the lead physician, statistician and study project manager or their equivalents.

18. REFERENCES

1. Anker SD, Colet JC, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009 Dec 17;361(25):2436-48. Epub 2009 Nov 17.

2. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J. 2015;36:657-68. Epub 2014 Aug 31.

3. Jankowska EA, Tkaczyszyn M, Suchocki T, Drozd M, von Haehling S, Doehner W, et al. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. Eur J Heart Fail. 2016. p. 1-16.

4. Jankowska EA, Kasztura M, Sokolski M, Bronisz M, Nawrocka S, Oleskowska-Florek W, et al. Iron deficiency defined as depleted iron stores accompanied by unmet cellular iron requirements identifies patients at the highest risk of death after an episode of acute heart failure. Eur Heart J. 2014;35:2468-76. Epub 2014 Jun 13.

5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129-200. Epub 2016 May 20.

6. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary. Circulation. 2013 Oct 15;128:1810-52.

7. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J. 2006;27:2725-36. Epub 2006 Sep 25. Authors are members of the EuroHeart Survey Investigators.

8. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, et al. Heart failure: preventing disease and death worldwide. ESC Heart Failure. 2014;1:4-25. Epub 2014 Aug 29.

9. Cotter G, Milo O, Davison BA. Increased mortality after an acute heart failure episode: new pathophysiological insights from the RELAX-AHF study and beyond. Curr Heart Fail Rep. 2014;11:19-30. Epub 2013 Dec 22.

10. Anderson GJ, Vulpe CD. Mammalian iron transport. Cell Mol Life Sci. 2009;66:3241–61. Epub 2009 May 31.

11. Cairo G, Bernuzzi F, Recalcati S. A precious metal: iron, an essential nutrient for all cells. Genes Nutr. 2006;1(1):25-39.

12. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, et al. Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J. 2013 Apr;165(4):575-82.e3.

13. Macdougall IC. Evolution of IV iron compounds over the last century. J Ren Care. 2009;35(s2):8-13.

14. Okonko DO, Mandal AKJ, Missouris CG, Poole-Wilson PA. Disordered iron homeostasis in chronic heart failure. Prevalence, predictors, and relation to anemia, exercise capacity, and survival. J Am Coll Cardiol. 2011 Sep 13;58(12):1241-51.

15. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol. 2012 Mar 13;59(11):998-1005.

16. Okonko DO, Anker SD. Anemia in chronic heart failure: pathogenetic mechanisms. J Card Fail. 2004;10(1 Suppl):S5-9.

17. González-Costello J, Comin-Colet J. Iron deficiency and anaemia in heart failure: understanding the FAIR-HF trial. Eur J Heart Fail. 2010;12:1159-62. Epub 2010 Sep 20.

18. Anker SD, Colet JC, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Rationale and design of Ferinject® assessment in patients with IRon deficiency and chronic Heart Failure (FAIR-HF) study: a randomized, placebo-controlled study of intravenous iron supplementation in patients with and without anaemia. Eur J Heart Fail. 2009;11:1084-91.

19. Bolger AP, Bartlett FR, Penston HS, O'Leary J, Pollock N, Kaprielian R, et al. Intravenous iron alone for the treatment of anemia in patients with chronic heart failure. J Am Coll Cardiol. 2006 Sep 19;48(6):1225-7. Epub 2006 Aug 28.

20. Okonko DO, Grzeslo A, Witkowski T, Mandal AKJ, Slater RM, Roughton M, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency. J Am Coll Cardiol. 2008 Jan 15;51(2):103-12.

21. Toblli JE, Lombraña A, Duarte P, Di Gennaro F. Intravenous iron reduces NT-Pro-Brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. J Am Coll Cardiol. 2007 Oct 23;50(17):1657-65.

22. Usmanov RI, Zueva EB, Silverberg DS, Shaked M. Intravenous iron without erythropoietin for the treatment of iron deficiency anemia in patients with moderate to severe congestive heart failure and chronic kidney insufficiency. J Nephrol. 2008;21:236-42.

23. Sandek A, Bauditz J, Swidsinski A, Buhner S, Weber-Eibel J, von Haehling S, et al. Altered intestinal function in patients with chronic heart failure. J Am Coll Cardiol. 2007 Oct 16;50(16):1561-9.

24. Silverberg DS, Wexler D, Iaina A. The role of anemia in congestive heart failure and chronic kidney insufficiency. Perspect Biol Med. 2004;47(4):575-89.

25. Wang J, Pantopoulos K. Regulation of cellular iron metabolism. Biochem J. 2011;434:365-81.

26. Stein J, Hartmann F, Dignass AU. Diagnosis and management of iron deficiency anemia in patients with IBD. Nat Rev Gastroenterol Hepatol. 2010 Nov;7:599-610. Epub 2010 Oct 5.

27. Gaillard CA, Bock AH, Carrera F, Eckardt KU, Van Wyck DB, Bansal SS, et al. Hepcidin response to iron therapy in patients with non-dialysis dependent CKD: an analysis of the FIND-CKD trial. PLoS ONE. 2016 Jun 8;11(6):e0157063. p. 1-15.

28. Jankowska EA, Malyszko J, Ardehali H, Koc-Zorawska E, Banasiak W, von Haehling S, et al. Iron status in patients with chronic heart failure. Eur Heart J. 2013;34:827-34. Epub 2012 Nov 23.

29. Jankowska EA, Wojtas K, Kasztura M, Mazur G, Butrym A, Kalicinska E, et al. Bone marrow iron depletion is common in patients with coronary artery disease. Int J Cardiol. 2015;182:517-22. Epub 2014 Oct 8.

30. Geisser P, Baer M, Schaub E. Structure/histotoxicity relationship of parenteral iron preparations. Arzneim-Forsch/Drug Res. 1992;42(12):1439-52.

31. Clinical study report VIT-IV-CL-001. A single-centre controlled isotope study of intravenous iron supplementation with 52-Fe(III)- and/or 59-Fe(III)-hydroxide dextrin complex (iron dextrinate, iron polymaltose) in iron deficient and in stable iron replete renal failure patients treated with erythropoietin, respectively. Final report. St. Gallen (Switzerland): Vifor (International) Inc.; 2003 Dec 8. Report No.: VIT-IV-CL-001.

32. Beshara S, Sörensen J, Lubberink M, Tolmachev V, Långström B, Antoni G, et al. Pharmacokinetics and red cell uitilization of 52Fe/59Fe-labelled iron polymaltose in anaemic patients using positron emission tomography. Br J Haematol. 2003;120:853-9.

33. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. Eur Heart J. 2010;31:1872-80. Epub 2010 Jun 21.

34. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J. 2001 Sep;22(17):1527-60.

35. Spertus JA, Jones PG. Development and validation of a short version of the Kansas City Cardiomyopathy Questionnaire. Circ Cardiovasc Qual Outcomes. 2015 Sep;8:469-76.

36. van Reenen M, Janssen B. EQ-5D-5L User guide. Basic information on how to use the EQ-5D-5L instrument. Version 2.1. 2015 Apr. Available from: http://www.euroqol.org.

37. O'Connor CM, Miller AB, Blair JEA, Konstam MA, Wedge P, Bahit MC, et al. Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction: results from efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan (EVEREST) program. Am Heart J. 2010 May;159(5):841-9.e1. Authors are members of the Efficacy of Vasopressin Antagonism in heart Failure Outcome Study with Tolvaptan (EVEREST) investigators.

38. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail. 2013;15:808-17. Epub 2013 Mar 287.

39. PASS 14 Power Analysis and Sample Size Software. NCSS, LLC. 2015.

40. Zhu H, Lakkis H. Sample size calculation for comparing two negative binomial rates. Stat Med. 2014;33:376-87. Epub 2013 Aug 23.

41. Rogers JK, Pocock SJ, McMurray JJV, Granger CB, Michelson EL, Östergren J, et al. Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. Eur J Heart Fail. 2014;16:33-40.

42. Liu L, Huang X. The use of Gaussian quadrature for estimation in frailty proportional hazards models. Stat Med. 2008;27:2665-83. Epub 2007 Oct 1.

43. World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. JAMA. 2013 Nov 27;310(20):2191-4.

44. EMEA European Medicines Agency. ICH Topic E6(R1): Guideline for good clinical practice. CPMP/ICH/135/95. 2002 Jul.

45. PhRMA. Principles on conduct of clinical trials and communication of clinical trial results. Washington (DC): Pharmaceutical Research and Manufacturers of America. 2014 Dec.

46. International Committee of Medical Journal Editors [Internet]. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals [updated 2015 Dec]. Available from: http://www.icmje.org.

Appendix 1 Serious Adverse Event Form (Sample)

Vifor Pharma

FORGDS027915: Serious Adverse Event Report Form V02

Study/Protocol ID: FER-CARS-06 (AFFIRM-AHF) **SUBJECT ID:** |_ _|_ _|_ _|_ _||_ _|_ _|_ _|_ _|_ _|

1. REPORT INFORMATION

Select: ☐ **Initial Report** or ☐ **Follow-up Report** (Enter Date: |_ _|_ _| - |_ _|_ _|_ _| - |_ _|_ _|_ _|_ _|)
DD MMM YYYY

2. SUBJECT INFORMATION:

a) Year of birth: |_ _|_ _|_ _|_ _| or if unknown, enter age at SAE onset: |_ _|_ _| years

b) Gender: ☐ Male or ☐ Female

c) Randomization number: |_ _|_ _|_ _|_ _|_ _|_ _|_ _|_ _|

d) Height: |_ _|_ _|_ _| ☐ cm or ☐ inches

e) Weight: |_ _|_ _|_ _| ☐ kilograms or ☐ pounds

3. STUDY DRUG ADMINISTRATION

Study drug treatment: ☐ NOT APPLICABLE ☐ BLINDED STUDY TREATMENT

Has the subject taken/received at least one dose of blinded study drug? ☐ NO or ☐ YES. If yes, please fill in following study drug administration details:

	V2 (Week 0)	V3 (Week 6)	V4 (Week 12)	V5 (Week 24)	Unscheduled visit
Start date and time of IV bolus injection	_____ (DD-MMM-YYYY) _ _: _ _ (HH24: MI)	_____ (DD-MMM-YYYY) _ _: _ _ (HH24: MI)	_____ (DD-MMM-YYYY) _ _: _ _ (HH24: MI)	_____ (DD-MMM-YYYY) _ _: _ _ (HH24: MI)	_____ (DD-MMM-YYYY) _ _: _ _ (HH24: MI)
Stop date and time of IV bolus injection	_____ (DD-MMM-YYYY) _ _: _ _ (HH24: MI)	_____ (DD-MMM-YYYY) _ _: _ _ (HH24: MI)	_____ (DD-MMM-YYYY) _ _: _ _ (HH24: MI)	_____ (DD-MMM-YYYY) _ _: _ _ (HH24: MI)	_____ (DD-MMM-YYYY) _ _: _ _ (HH24: MI)

4. ACTION TAKEN WITH STUDY DRUG:

- ☐ =None/Dose not changed
- ☐ =Temporary interrupted, please record the Date and Time: _____ (DD-MMM-YYYY)/ _ _:_ _ H24:MI
- Did the treatment re-start: ☐ Yes ☐ No
  Please record the Date and Time: _____ (DD-MMM-YYYY)/ _ _:_ _ H24:MI
- ☐ =Permanently discontinued
  Please record the Date and Time: _____ (DD-MMM-YYYY)/ _ _:_ _ H24:MI
- ☐ =Not applicable
- ☐ =Unknown

Did the SAE(s) improve or resolve after stopping or reducing study drug? ☐ No ☐ Not applicable ☐ Unknown

☐ Yes. If yes, please provide the SAE number(s) from section 6: _____

Did the SAE(s) recur after study drug was restarted? ☐ No ☐ Not applicable ☐ Unknown

☐ Yes. If yes, please provide the SAE number(s) from section 6: _____

5. SERIOUS ADVERSE EVENT (SAE) DESCRIPTION *(Please describe the clinical course of events, incl. signs, symptoms, most important reactions, final (or working) diagnosis, all relevant laboratory tests and findings and treatment. If any associated medical records are available (i.e. hospital discharge summary, autopsy report, death certificate), please attach a copy along with this report).*

Study/Protocol ID: FER-CARS-06 (AFFIRM-AHF) **SUBJECT ID:** |_ _|_ _|_ _|_ _||_ _|_ _|_ _|_ _|_ _|_ _|

6. SERIOUS ADVERSE EVENT DETAILS: **Please indicate how many pages for describing SAE Details are used for this Report: 1 or 2 or 3**

Is any of these SAEs proposed for adjudication? ☐ No ☐ Yes, please indicate SAE No.: _____

SAE No.	**SAE Term(s)** (*Please provide diagnosis {single illness or syndrome} instead of symptoms)*	**SAE Start date/time** Add DD-MMM-YYYY/HH24 MI	**SAE Stop date** Add DD-MMM-YYYY Or tick "ongoing" ☐ Or "Unknown" ☐	**Severity:** Add 1=Mild 2=Moderate 3 =Severe	**Other Action taken** 0=None; 1=Medication given; 2=Procedure given; 3=Early study termination	**Outcome** 1=Recovered/resolved (without sequelae) 2=Recovered/resolved with sequelae, also specify the kind of sequelae 3=Recovering/resolving 4=Not recovered/not resolved 5=Fatal 6=Unknown, also specify the rational for unknown.	**SAE Criteria** 1=Results in death 2=Is Life threatening 3=Requires or prolongs hospitalisation 4=Results in persistent or significant disability/ incapacity 5=Is a congenital anomaly/ birth defect 6=Other important medical event [If SAE resulted in death, please complete information on the next page in table (a))]. [If hospitalisation, please provide the dates on the next page in table (b)]	**Relationship to study drug** 0=Certain 1=Probable /Likely 2=Possible; 3=Unrelated

6. SERIOUS ADVERE EVENT DETAILS - SAE Criteria (continued)

a) If the subject died, record the possible causes of death under SAE term above OR if the cause of death is unknown insert "Death due to unknown cause" as SAE term.

Date of death: |_ _|_ _| - |_ _|_ _|_ _| - |_ _|_ _|_ _|_ _|

Autopsy done: ☐ Unknown ☐ No ☐ Awaiting result ☐ Yes. If Yes, please provide the official cause of death:

_____

b) Date of hospital admission: |_ _|_ _| - |_ _|_ _|_ _| - |_ _|_ _|_ _|_ _|

Date of discharge: |_ _|_ _| - |_ _|_ _|_ _| - |_ _|_ _|_ _|_ _| or ☐ Not applicable (check this only for death)

7. SPECIAL SITUATION(S):

a) Did any Special Situation occur with the study drug (administration)?

☐ **No** ☐ **Yes.** If Yes, please enter the appropriate special situation code(s): _____

001=Medication error; 002=Medication Misuse; 003=Medication Abuse; 004=Occupational exposure; 005=Drug interaction; 006=Unexpected therapeutic or clinical benefit from product use; 007=Medication Overdose; 008 = Exposure during pregnancy or breast feeding.

If "Exposure during Pregnancy", fill in the "Report on Exposure to Medicines during Pregnancy", and send/fax it within 24 hrs following the safety reporting instructions as outlined in the trial protocol.

b) Was any Special Situation associated with any (serious) adverse event(s)?

☐ **No** ☐ **Yes.** If Yes, please complete the AE-CRF page and (if serious) Section 6 of the Serious Adverse Event Form.

c) Has the subject discontinued from the trial due to any Special Situation:

☐ **No** ☐ **Yes.** If Yes, specify reason:

_____

Provide a brief description of the clinical course of the Special Situation(s) in chronological order.

8. RELEVANT MEDICAL HISTORY and CONCOMITANT MEDICATIONS/PROCEDURES

- Has the subject had any relevant medical and surgical history or any co-existing diseases? ☐ **No** ☐ **Yes.**
  If Yes, please complete the table below:

Condition	Start date	Stop date	Ongoing

- Has the subject received any Concomitant Medication(s) or Procedures? ☐ **No** ☐ **Yes**.
  If Yes, please complete the table below:

Name of medication	Start date	End date/Ongoing	Indication for use	Dose	Frequency	Route of administration

9. REPORTER INFORMATION:

Site number: |_ _|_ _|_ _|_ _| **Country:** _____

Reporting Date: |_ _|_ _| - |_ _|_ _|_ _| - |_ _|_ _|_ _|_ _|

Reporter:

_____ _____

Print Reporter's Name **Reporter's signature**

_____ _____

Fax number Phone number

Investigator (if different from Reporter):

_____ _____

Print Investigator's Name **Investigator's signature**

In case of technical problems with the EDC system,

please complete this SAE Report Form and transmit it immediately to WCT via:

FAX: [redacted]

(or E-mail: [redacted]

Appendix 2 Report on Exposure to Medicines During Pregnancy (Sample)

Vifor Pharma

FOR GDS 171: PREGNANCY REPORT V01

REPORT ON EXPOSURE TO MEDICINES DURING PREGNANCY Part 1

Name of Vifor Drug (Trade name / IMP): _____

Clinical Trial Protocol Identifier (if applicable): _____

Patients Initials / No: _____ Country: _____ Local Reference No: _____

Details of Mother and Pregnancy

Date / Year of Birth: / / (dd/mmm/yyyy) Age: Occupation:

Previous Pregnancy

Yes ☐ No ☐ Total no. of pregnancies: _____ Normal Deliveries: _____

Abortions (Spontaneous): _____ Abortions (performed): _____

Relevant Medical History:
(including pregnancy risk factors, Pre-eclampsia, eclampsia, smoking, alcohol, environmental & occupational exposures etc.)

Relevant Family History:
(hereditary diseases e.g. hypertension, diabetes)

Current Pregnancy

First day of Last Menstruation: / / (dd/mmm/yyyy) Expected Delivery Date: / / (dd/mmm/yyyy)

Gestational age of foetus (specify at time of exposure / time of reporting) : _____

Ultrasound performed? Yes ☐ No ☐ If yes, findings if any: _____

Any complications, infections or illnesses during pregnancy? Yes ☐ No ☐

If yes, elaborate: _____

Drug Exposure during Pregnancy

Mother /Father Exposure	Suspect Drug/ Concomitant medication	Product Name (Trade / IMP) Batch no.	Total Daily Dose (Units)	Therapy Start date	Therapy Stop date	Indication for use	Route of application (oral, infusion, injection)

_____ _____

Place, Date (dd/mmm/yyyy) **Name/ Signature/Stamp of Reporter**

REPORT ON EXPOSURE TO MEDICINES DURING PREGNANCY Part 2

Information on Outcome of Pregnancy

Name of Vifor Drug (Trade name/IMP)**:** _____

Clinical Trial Protocol Identifier (if applicable): _____

Patients Initials / No: _____ Country: _____ Local Reference No: _____

Outcome of Pregnancy

☐ Full Term — Normal delivery or Caesarean: _____

☐ Premature Birth — If premature birth, gestational age: _____ weeks

☐ Spontaneous Miscarriage

☐ Elective termination — Medical Reason? ☐ Yes ☐ No

If yes, specify: _____

Details / Comments (if any): _____

☐ Healthy Baby ☐ Multiple Births

☐ Sick Baby (e.g. Birth trauma, infection etc.) ☐ Congenital anomaly or Birth defect ☐ Still Birth

Date of Birth ___/___/_____ (dd/mmm/yyyy) Sex ☐ Male ☐ Female

Size: _____ Weight: _____ APGAR scores, if provided (Birth/5/10 mins.) _____

Details / Comments (if any): _____

Please comment on any abnormal condition or occurrence regarding outcome of pregnancy and/or birth/delivery.

Is there a suspicion that adverse outcome of pregnancy is related to exposure to Product?

☐ Yes ☐ No

Please elaborate: _____

_____ _____

Place, Date (dd/mmm/yyyy) **Name/ Signature/Stamp of Reporter**

Please always send both Part I and Part II of the form to [redacted]
or fax to: [redacted]

Appendix 3 Guidelines for Administering Informed Consent

These guidelines apply to all study site personnel administrating informed consent to a potential subject *or* their legally acceptable representative, which must be done ***prior*** to conducting any study related functions, including verifying eligibility.

These guidelines are to be used when your site IRB does not provide you with an equivalent documented consent process; or when your site does not have an equivalent written process (like an SOP).

1. Present the potential subject or legally acceptable representative with:
   - The most up-to-date version of the IRB/REB/EC approved informed consent form (ICF)
   - The Subject Information Sheet (PIS) (if any)

2. Explain the following to the potential subject:
   - That the trial involves research
   - The purpose of the trial
   - The trial treatments, procedures to be followed and (if randomized) the probability of each treatment
   - Alternative procedures or treatment that may be available
   - The subject's responsibilities
   - All aspects of the trial which are experimental
   - Reasonably foreseeable risks
   - Reasonably expected benefits
   - Compensation and/or treatment available in the event of trial-related injury
   - Anticipated payment to the subject, and expenses (if applicable)
   - The subject's participation is voluntary; the subject may withdraw consent at anytime. In the USA and whenever poss ble the withdrawal of consent must be done in writing.
   - Monitor(s), auditor(s) and the IRB/EC and Regulatory Authorities may be allowed direct access to the subjects' medical records.
   - Records identifying the subject will be kept confidential
   - If any information becomes available which may be relevant to the subject's willingness to continue in the trial, he/she should be informed in a timely manner
   - The person(s) to contact for further information regarding the trial and the subject's rights
   - The foreseeable circumstances and/or reasons whereby the subject may be withdrawn from the trial
   - The foreseeable circumstances and/or reasons whereby the trial may be terminated
   - The expected duration of the subject's participation in the trial
   - The approximate number of subjects in the trial

3. Throughout the process, ensure that:

   - The potential subject is not coerced or unduly influenced to participate in the trial

- There is ample opportunity and time for the subject to ask questions and to receive satisfactory answers.
- If the subject (or representative) is unable to read, an impartial witness is present during the entire consent discussion. By signing the consent form, the witness confirms that the trial was fully explained and verbal consent willingly given.
- The consent form is **signed** and **dated** by the subject (or representative), the person explaining the study and the witness (if applicable).
- The subject (or representative) receives a copy of the signed and dated consent form and all other written subject information.

IT IS THE PRINCIPAL INVESTIGATOR'S RESPONSIBILITY TO DOCUMENT THIS PROCESS

4. Tips on documentation of the informed consent process

- There should be a "contextual" statement in the source document to show exactly how and when IC was administered - including the time (even if it is on the ICF).