STATISTICAL ANALYSIS PLAN
Protocol FER-CARS-06
EudraCT Number: 2016-001467-36

A Randomised, Double-blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure (AFFIRM-AHF)

Protocol Number:	FER-CARS-06
(Version Date)	Version 3.1 (1 April 2020)
Name of Test Drug:	IV Ferric carboxymaltose (FCM)
Phase:	4, therapeutic use
Methodology:	Double-blind, randomised, placebo-controlled
Sponsor:	Vifor (International) Inc. Rechenstrasse 37 St. Gallen CH-9001 Switzerland
Sponsor Representative:	[redacted] Chief Medical Officer
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SIGNATURE PAGE

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Cytel, Inc. Authors: [redacted] Cytel, Inc. 20 route de Pre-Bois CH-1216 Cointrin	Signature:____ Date and time____

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatory: [redacted] Head of Biometrics	Signature:____ Date and time:____
[redacted] Chief Medical Officer	Signature:____ Date and time:____

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ABBREVIATIONS

Abbreviation	Definition
AHF	Acute heart failure
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass surgery
CI	Confidence interval
CEC	Clinical Endpoint Committee
CKD	Chronic Kidney Disease
CRT	Cardiac resynchronization therapy
CSR	Clinical Study Report
CV	Cardiovascular
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EQ-5D	European Quality of Life – 5 Dimensions
FAS	Full Analysis Set
FCM	Ferric carboxymaltose
GCP	Good Clinical Practice
GEE	Generalized estimating equations
Hb	Haemoglobin
HLT	High Level Term
HF	Heart failure
HRQoL	Health-related quality of life
ICD	Implantable cardioverter defibrillator
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Iron deficiency
IMP	Investigational medicinal product
IV	Intravenous
IWRS	Interactive Web Response System
K	Dispersion factor
KCCQ-12	Kansas City Cardiomyopathy Questionnaire-12
KM	Kaplan-Meier
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
NTproBNP	N-terminal-probrain natriuretic peptide

Abbreviation	Definition
NYHA	New York Heart Association
OR	Odds ratio
PCI	Percutaneous coronary intervention
PP	Per-Protocol
PT	Preferred Term
QoL	Quality of life
Q1	First quartile
Q3	Third quartile
QTcB	Heart rate-adjusted (ECG) QT interval – Bazett's formula
QTcF	Heart rate-adjusted (ECG) QT interval – Fridericia's formula
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Standard deviation
SD1	Study Day 1
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TSAT	Transferrin saturation
TTO	Time trade-off
VAS	Visual analogue scale
WHO	World Health Organization

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

Acute Heart Failure (AHF) constitutes a clinically and economically challenging problem. The prognosis of subjects with AHF remains poor, and so far, major clinical trials have failed to improve outcomes in these subjects. The current treatment of AHF has remained virtually unchanged in recent decades. Iron Deficiency (ID) is frequent among subjects with Heart Failure (HF) and predicts poor outcome [1]. Although there are suggestions that correction of ID in AHF subjects could improve clinical outcomes, this has not been investigated to date.

FER-CARS-06 is a phase 4, randomised, double-blind, placebo controlled trial comparing the effect of IntraVenous (IV) Ferric CarboxyMaltose (FCM) on hospitalisations and mortality in iron-deficient subjects admitted for AHF. The aim of the study is to investigate the effect of IV FCM relative to placebo on recurrent HF hospitalisations and CardioVascular (CV) death up to 52 weeks after randomisation in iron-deficient subjects hospitalised for AHF.

1.2. Objectives of Statistical Analysis

1.2.1. Objectives of the Study

Primary

To evaluate, relative to placebo, the effect of IV FCM on the composite of repeated HF hospitalisations and CV death.

Secondary

To evaluate, relative to placebo, the effect of IV FCM on:

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

1.2.2. Objectives of the SAP

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to address the study objectives. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the Clinical Study Report (CSR) for this trial.

This SAP also will outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

This SAP has been prepared in conjunction with protocol version 3.1 (date: 01Apr2020).

2. STUDY DESIGN

2.1. Synopsis of Study Design

This is a phase 4, randomised, double-blind, placebo-controlled trial. The 52-week observation period following randomisation is considered appropriate to investigate the primary endpoint of the composite 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. First study drug will be administered in the hospital prior to discharge for the index hospitalisation. Over the 52 weeks following randomisation, the collected endpoints will focus on important events for this subject population (hospitalisations, mortality and QoL) that directly impact the subjects and the health care system.

2.2. Randomisation Methodology

This is a double-blind trial with randomisation concealment, and neither the Investigator, the subject, nor the Sponsor (or representative) will be aware of the study drug allocated to each subject. The FCM and placebo solutions differ in appearance. Hence, unblinded study personnel not otherwise involved in any study assessments (efficacy or safety) will be responsible for preparing and administering the study drug injections. At the site level, study drug will be prepared by the unblinded team and assessments during follow-up will be done by the blinded team only. The Vifor Pharma Safety Department will have access to the randomisation codes, as will Investigational sites should the need to unblind a subject arise.

Each eligible subject will be randomised to either FCM or placebo using a validated centralised procedure [Interactive Web Response System (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 (ischaemic/non-ischaemic/unknown), HF duration (newly diagnosed at Index hospitalisation/known documented HF prior to Index hospitalisation), country, and centre. The system will allocate study drug 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.

A total of 1,100 subjects (550 per treatment group) will be randomised into the study.

2.3. Stopping Rules and Unblinding

A subject's treatment assignment must be unblinded only when knowledge of the treatment is essential to make a decision on the medical management of the subject or a subject's treatment allocation is required for regulatory reporting purposes. Unblinding for any other reason will be considered a protocol deviation.

If a study drug code is broken, the subject concerned must discontinue study drug. 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.

2.4. Study Procedures

The Schedule of Events and the Flow Chart are shown in Table 1 and Figure 1.

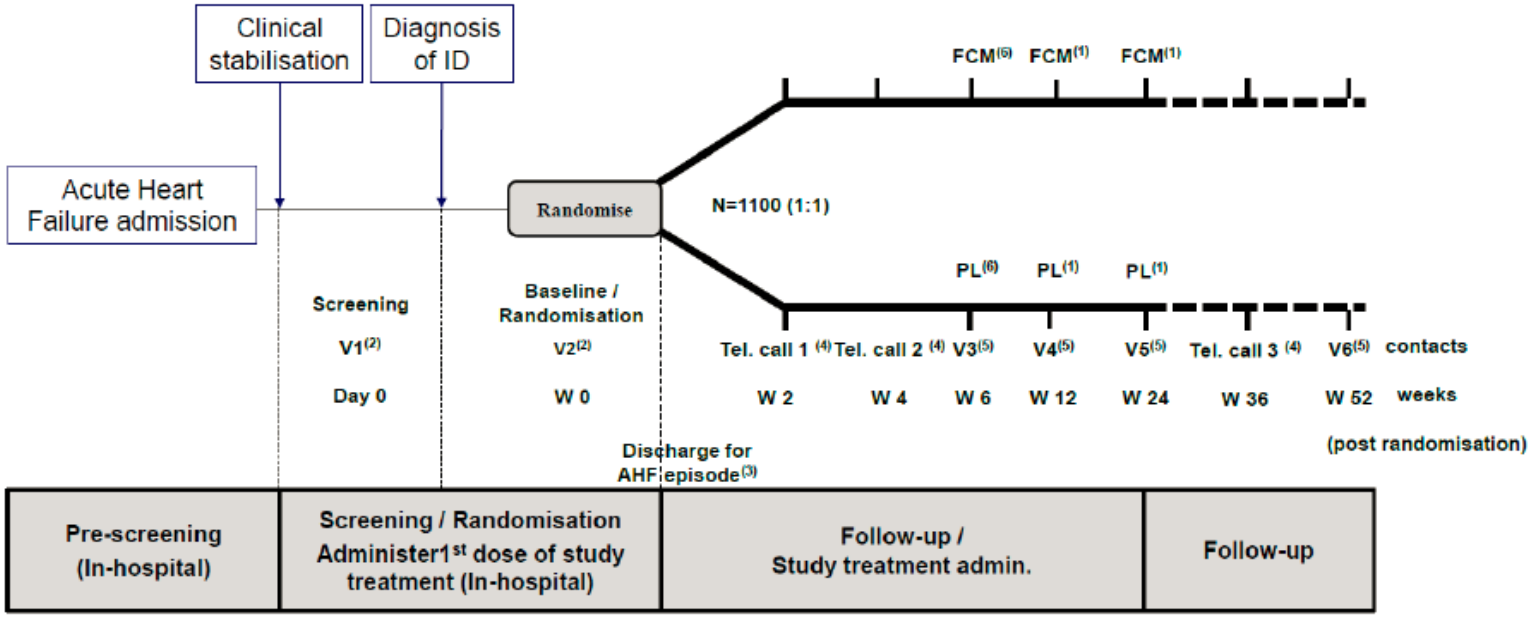
Table 1 Schedule of Events

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
Randomisation		X[8]								
Administer study treatment[9]		X[10]			X[11]	X[12]	X[12]		(13)	(13)

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	
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 seous 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 (**Error! Reference source not found.**). 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.

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.

2.5. Efficacy, Pharmacokinetic, and Safety Variables

2.5.1. Primary Endpoint

The composite of recurrent HF hospitalisations and cardiovascular (CV) death up to 52 weeks after randomisation.

2.5.2. Secondary Endpoints

If the null hypothesis regarding the primary endpoint can be rejected at the two-sided significance level of 5%, Hochberg's procedure will be used to control the overall Type I error (familywise Type I error rate; FWER) at the same level 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 a recurrent event).
- CV mortality analysed as time to first event up to 52 weeks after randomisation.
- The composite of HF hospitalisations or CV death analysed as time to first event up to 52 weeks after randomisation.
- Days lost due to HF hospitalisations or CV death up to 52 weeks after randomisation.

NOTE: Adjudication will also be performed for emergency room admissions and unscheduled outpatient clinic visits to treat worsening HF ('urgent heart failure visits'). All primary and secondary endpoints will be analysed excluding urgent heart failure visits.

2.5.3. Other Endpoints

- 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 up to 30 days after randomisation.
- The composite of CV hospitalisations or CV death analysed as time to first event up to 30 days after randomisation.
- HF hospitalisations up to 30 days after randomisation (analysed as a recurrent event).
- HF hospitalisations up to 30 days after randomisation (analysed as time to first event).
- HF hospitalisations up to 52 weeks after randomisation (analysed as time to first event).
- CV hospitalisations up to 30 days after randomisation (analysed as a recurrent event and time to first event).
- CV hospitalisations up to 52 weeks after randomisation (analysed as a recurrent event and time to first event).
- The composite of CV hospitalisations or CV death analysed as time to first event up to 30 days after randomisation.
- The composite of CV hospitalisations or CV death analysed as time to first event up to 52 after randomisation.
- CV mortality analysed as time to first event up to 30 days after randomisation.
- All-cause mortality analysed as time to first event up to 30 days after randomisation.
- All-cause mortality analysed as time to first event up to 52 weeks after randomisation.
- Proportion of subjects 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 (KCCQ-12) Overall Summary Score, Clinical Summary Score and Physical Summary Score to weeks 2, 4. 6, 12, 24, 36 and 52 after randomisation.

- Percentage of subjects with improvement of ≥ 5 or ≥ 8 points and percentage of subjects with ≥ 5 points deterioration from baseline in KCCQ-12 Overall Summary Score, Clinical Summary Score and Physical Summary Score to weeks 2, 4, 6, 12, 24, 36 and 52 after randomisation.
- Change from baseline in the European Quality of Life – 5 Dimensions questionnaire indexed value and VAS at weeks 6, 24 and 52 after randomisation.
- Days lost due to HF hospitalisations or CV death up to 30 days after randomisation.

  NOTE: Adjudication will also be performed for emergency room admissions and unscheduled outpatient clinic visits to treat worsening HF ('urgent heart failure visits'). All endpoints mentioned in the section of other endpoints that include HF hospitalisations will be analysed including and excluding urgent heart failure visits. In addition, all endpoints mentioned in the sections of primary endpoint and secondary endpoints that include HF hospitalisations will also be analysed including urgent heart failure visits as other endpoints.

2.5.4. Safety Endpoints

- Incidence of adverse events (AEs): by System Organ Class (SOC) and Preferred Term (PT) (Medical Dictionary for Regulatory Activities (MedDRA) coded term), by maximum severity, related to study drug, leading to study drug discontinuation, serious, leading to death, and adjudicated.
- Incidence of AEs of clinical interest: HF hospitalisation and CV death.
- Incidence of Special Situation Events.
- Incidence of event adjudication (Hospitalisation, Urgent HF visit and Deaths).
- Incidence of related AEs of special interest: Hypersensitivity reactions, Hypophosphatemia, Injection/infusion site reactions and Haemosiderosis.
- Clinical laboratory panels (absolute and change from baseline, incidence of laboratory abnormalities).
- Vital Signs (absolute and change from baseline).
- Electrocardiograms (incidence of electrocardiogram abnormalities, QTc measurement meeting ICH E14 criteria [2]).
- Prior, concomitant and newly started medications.

Note: biomarkers exploratory analyses will not be part of the CSR of the main study. They will be described in a separate biomarker SAP.

3. ANALYSIS POPULATIONS

3.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

Screened population

The screened population will consist of all subjects who signed an informed consent form.

All Randomised

The All Randomised set will consist of all subjects randomised to either of the two treatment groups. The All Randomised set will be analysed based on the randomised treatment arm.

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, and
- The administration of study drug was started.
- At least one post-baseline visit (including calls), death or hospitalisation or subjects without post-baseline assessment who withdrew from the study after but not on the randomisation date.

Additionally, subjects with protocol deviation concerning inclusion criteria no. 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*.) will be excluded from FAS.
Subjects in the FAS will be analysed based on their randomised treatment arm.

Per-Protocol Set

The Per-Protocol (PP) analysis set will consist of all subjects in the FAS who had no major protocol violations (see Appendix I).

Safety Set

The Safety (SAF) analysis set will consist of all randomised subjects for whom the administration of study drug has started. Subjects will be analysed according to the treatment received.

The analysis sets to be used for analyses are described in the table below.

Table 2 Analysis Sets

Analyses	Screened population	All Randomised	FAS	PP	SAF
Subject disposition	✓	✓			
Protocol deviations/violations		✓			
Demographics			✓	✓	✓
Baseline characteristics (prior, concomitant and newly started medications, medical history including surgical history and procedures)			✓	✓	✓
Prior medications, concomitant, newly started medications			✓		✓
Medical History and history of cardiovascular factors.			✓	✓	✓
Compliance and exposure					✓
Primary endpoint			✓	✓	
Secondary endpoints			✓	✓	
Other endpoints			✓	✓	
KCCQ-12			✓	✓	
EQ-5D			✓	✓	
AEs, SAEs, and special situations					✓
Event Adjudications					✓
Laboratory parameters					✓
ECGs					✓
Vital Signs					✓

3.2. Protocol Deviations/Violations

The sponsor, or designee, will be responsible for producing the final protocol deviation/violation file (formatted as an Excel file or SAS dataset), in collaboration with Cytel and the data monitoring group as applicable; this file will include a description of each protocol deviation/violation, and will clearly identify whether or not each violation warrants exclusion from a population. This file will be finalized prior to hard database lock.

Protocol deviations will be reported in a data listing for all subjects in the All randomised.

4. STATISTICAL METHODS

4.1. Sample Size Justification

The recurrent HF hospitalisation and CV death rates in the control group were extrapolated as 0.9 events/year using the data from the EVEREST study [3] and as 0.61 events/year using the data from the ESC-HF study [4]. For this study, it is anticipated that approximately 35% of subjects will sustain either a CV death or 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 estimating the average number of HF hospitalisations per subject with at least one HF hospitalisation as 2, the number of events per 100 years of follow-up 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 are 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 [5], using the sample size formula proposed by Zhu and Lakkis 2014 [6] to compare two negative binomial rates.

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

4.2. General Statistical Methods and Data Handling

4.2.1. General Methods

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category of the parameter will be presented (with a category for missing data if appropriate). For continuous variables, the mean, median, standard deviation (SD), first and third quartiles (Q1 and Q3), and minimum and maximum values will be presented. The level of significance to be used for tests will be 0.05, two-sided.

Listings will be sorted by subject ID unless specified otherwise.

Label of the group treated with Intra Venous Ferric CarboxyMaltose will be "FCM", placebo group will be labelled as "Placebo".

All outputs will be incorporated into Word files, sorted and labelled according to the International Council for Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

4.2.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4 or later), unless otherwise noted. Medical history and adverse events will be coded using MedDRA. Medications will be coded using the World Health Organization (WHO) Drug dictionary. Versions of dictionaries will be indicated in the footnote of the relevant tables and listings.

4.2.3. Methods of Pooling Data

AFFIRM-AHF database will be pooled with FAIR-HF2 (ClinicalTrials.gov Identifier: NCT03036462) and FAIR-HFpEF (ClinicalTrials.gov Identifier: NCT03074591) studies and integrated analyses will be performed:

- Integrated analysis 1: AFFIRM-HF and FAIR-HF2 studies
- Integrated analysis 2: AFFIRM-HF, FAIR-HF2 and FAIR-HFpEF studies

Specific integrated SAPs will be written for this purpose.

4.2.4. Adjustments for Covariates

Adjustments will be made for the following baseline covariates as measured at time of randomisation: sex, age, HF aetiology (ischaemic/non-ischaemic/unknown), HF duration category (newly diagnosed at Index hospitalisation/known documented HF prior to Index hospitalisation) and country. If there are too few subjects in some countries, country can be replaced for the adjustments by region as described in section 4.5.1.

4.2.5. Multiple Comparisons/Multiplicity

There will be no adjustment for multiplicity.

4.2.6. Subpopulations

Some analyses will be performed on the following subgroups:

- Hb level at baseline (< 12, ≥ 12 g/dL).
- Ferritin level at baseline by tertiles.
- Ferritin level at baseline (< 100 ng/mL, ≥ 100 ng/mL).
- TSAT category at baseline by tertiles.
- TSAT category at baseline (< 20%, ≥ 20%).
- Sex.
- Age by tertiles.
- Renal function at baseline defined as No CKD, CKD stages I and II, and CKD stages III, IV, or V at baseline medical history.
- Estimated glomerular filtration rate (eGFR) value at baseline by tertiles. The eGFR value at baseline will be calculated using the CKD-EPI formula and the baseline creatinine value.
- Ischaemic Aetiology of HF (ischaemic, non-ischaemic).
- NYHA at baseline (NYHA II, NYHA III, if applicable, i.e. if there are at least 10% of subjects by NYHA class and treatment group. NYHA I and IV not included).
- NT-pro BNP (pg/mL) or BNP (pg/mL) at baseline assigned to First tertile, Second tertile or Third tertile. Tertiles of NT-proBNP and BNP at baseline in FAS regardless of treatment group will be computed (for each parameter separately) and subjects will be assigned to these groups. In case subject has both values collected at baseline, NT-proBNP will be used and subject will be assigned according to computed NT-proBNP tertiles.
- Left ventricular ejection fraction (%) at baseline Left ventricular ejection fraction (LVEF) < 25%, ≥ 25% until < 40%, and ≥ 40% until < 50%
- Diagnosis of Heart Failure (newly diagnosed at index hospitalisation, known documented HF prior index hospitalisation).
- Subjects hospitalised for an episode of Acute Heart Failure in the previous 12 months prior Index Hospitalisation (yes, no).
- Creatinine at baseline by tertiles.

For subgroups defined by tertiles, tertiles will be computed on the FAS regardless of treatment group.

Additionally, following subgroups will be investigated for exploratory purposes:

- Geographical region (Latin America [Argentina, Brazil], Asia [Israel, Lebanon, Singapore], South and Eastern Europe [Italy, Croatia, Georgia, Romania, Ukraine], Central and Western Europe [Netherlands, Poland, United Kingdom, Spain, Sweden])
- Subjects with ARNI (yes, no)
- Subjects with ACE or ARB or ARNI, at least one of these groups (yes, no)
- Subjects with beta-blockers (yes, no)
- Subjects with Aldosterone Antagonists (yes, no)
- Subjects with triple therapy (defined as ACE or ARB or ARNI (any of these groups) and beta blockers and Aldosterone Antagonists) versus subject without the triple therapy

See section 4.8.8 and Appendix IV for definition of the medication of special interest categories. Medications will be considered for these subgroups if they were taken by the subject at the time of randomisation. Analyses for these six subgroups will not be part of the main set of outputs.

4.2.7. Withdrawals, Dropouts, Lost to Follow-up

Subjects who withdraw from the study will not be replaced.

4.2.8. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points, unless otherwise specified (see sections 4.6, 4.8.2 and 4.8.8). All data recorded on the electronic Case Report Form (eCRF) will be included in data listings that will accompany the Clinical Study Report.

4.2.9. Visit Windows

For summaries by timepoint, the time windows given in Table 3 will be applied to allocate measurements to analysis visit. This will be done for laboratory parameters, vital signs, ECG, NYHA Classification, KCCQ-12, and EQ-5D.

In general, in case multiple measurements are collected in the same window, the value closest to the target day as specified in Table 3 will be used for analysis. If there are 2 values with the same time before and after the target day, the later value will be used for analysis. If there are 2 continuous values on the same date then the average of the values will be used. For categorical variables, if there are more than 1 value on the same date then the worst case will be chosen (e.g. for EQ-5D).

Table 3 Analysis Assessment Windows

Parameter	Visit Label	Analysis Assessment Window (Efficacy/Safety)
Laboratory parameters, Vital signs, ECG, NYHA Classification	Baseline	≤1 day
	Week 6	Day 43 [2; 64] days
	Week 12	Day 85 [65; 107] days
	Week 24	Day 169 [108; 253] days
	Week 52	Day 365 [254; 408] days
EQ-5D	Baseline	≤1 day
	Week 6	Day 43 [2; 85] days
	Week 24	Day 169 [86; 253] days
	Week 52	Day 365 [254; 408] days
KCCQ-12	Screening	N/A
	Baseline	≤1 day
	Week 2	Day 14 [2; 20] days
	Week 4	Day 28 [21; 34] days
	Week 6	Day 43 [35; 64] days
	Week 12	Day 85 [65; 107] days
	Week 24	Day 169 [108; 211] days
	Week 36	Day 253 [212; 295] days
	Week 52	Day 365 [296; 408] days

4.2.10. Handling of Missing and Partial Dates

Imputation of missing and partial event dates, such as hospitalisation, AE and concomitant medication start and stop dates, is described in sections 4.6, 4.8.2 and 4.8.8.

4.2.11. Definition of First Study Day (SD1)

First study day (SD1) is defined as the date of first administration of IV FCM or placebo.

For efficacy assessments, study day will be computed from the randomisation into the study.

4.2.12. Definition of Baseline

Baseline is defined as the last non-missing assessment prior to or at SD1. More specifically, baseline is defined as the last record or measure collected prior to the first dose of investigational medicinal product (IMP).

If an assessment is collected on SD1 and either time of assessment or time of first dose is missing, then such assessment is considered as prior to the first dose. The exception for this rule are medications and AEs, which will be considered as concomitant or treatment-emergent, respectively.

4.2.13. End of Study (Last Visit)

End of study is defined as the date of the Week 52 visit for subjects completing the study, or the date of the early study termination visit for other subjects.

In cases where the subject dies, if the last visit is reported after death then death date will be used as last day in study.

4.2.14. Time on Study

Time on study for safety purposes is calculated for each subject from SD1 to the last known date:

Time on study (days) = (Last Known Date - SD1) + 1.

Time on study for efficacy purposes is calculated for each subject from randomisation date to the last known date:

Time on study (days) = (Last Known Date – Randomisation Date) + 1.

If last known date is outside of visit window for Week 52 visit (i.e. after study day 375), time on study will be 375 days for such subjects and only events up to this day will be considered.

4.2.15. Time on Study Drug

Time on study is calculated for each subject from SD1 to the date of last study drug injection:

Time on study drug (days) = (Last Study Drug injection date - SD1) + 1

4.2.16. Last Available Value

The last available value is defined as the last available value across visits, including unscheduled measurements.

4.2.17. Time since Initial Diagnosis

Time since initial diagnosis is calculated in years for each subject with known documented HF prior to index hospitalisation as the time since the diagnosis was made as of the informed consent date.

Time since diagnosis (years) = (Informed consent date – date of diagnosis + 1)/365.25

In case the diagnosis date is completely missing, the time since diagnosis will be missing. Otherwise, if the year and month are not missing, then the day will be set to 1. If the day and month are both missing, they will be set to 01JAN.

4.2.18. Subject-Years of Time on Study

Subject-years of time on study is the sum of all subjects' times on study (overall or by treatment groups) expressed in years.

> Subject-years of time on study = [Sum_i(time on study in days)] / 365.25, i=1 to n, where n is the number of subjects.

Note: for 30-days analysis, the time on study will be up to 30 days after randomisation.

4.2.19. Conversion Factors

The following conversion factors will be used to convert days into months or years, or vice versa:

- 1 week = 7 days,
- 1 month = 30.4375 days, and
- 1 year = 365.25 days.

The following conversion factors will be used for height and weight:

- 1 cm = 0.39370 in, and
- 1 kg = 2.20462 lb.

4.3. Interim Analyses

None are planned.

4.4. Subject Disposition

Subject disposition will be tabulated based on the screened population and will include the number screened subjects, randomised subjects, screened failures and subjects re-screened and randomised. If subject is re-screened, such subject will be calculated only once in the screened population. The reason for screen failure will be provided. All screen failure reasons including reasons if subject was re-screened, will be summarized.

In addition, the number of subjects randomised, treated, started treatment after and not on the randomisation date, randomised not-treated, who received a different treatment that they were randomised to, who discontinued treatment, discontinued study, discontinued treatment but completed study along with the reason for treatment discontinuation and the reason for study discontinuation will be provided based on All Randomised Set. The number of subjects in each population with reason for exclusion will be provided based on All Randomised population.

A by-subject listing of study withdrawal/completion information, including the reason for premature study withdrawal, if applicable, will be presented.

Protocol deviations will be listed.

In addition, Kaplan-Meier (KM) curves for time to discontinuation, censoring at last visit (see section 4.2.13), will be plotted by treatment group for the FAS.

4.5. Demographic and Baseline Characteristics

Demographic and baseline characteristics and medical history will be summarized for the FAS, PP, and SAF sets by treatment group using descriptive statistics. No formal statistical comparisons will be performed. All demographic and baseline characteristics will be provided in data listings.

4.5.1. Demographics

Demographics will include country, region (Latin America [Argentina, Brazil], Europe [Croatia, Georgia, Germany, Italy, Netherlands, Poland, Switzerland, United Kingdom, Romania, Spain, Sweden, Ukraine], Rest of the World [Israel, Lebanon, Singapore]), age at time of randomisation (years), randomisation age category (<18, 18-64, 65-84, >=85 years and <70 years vs. >=70 years), sex, ethnicity (Hispanic or Latino/a or of Spanish origin, not Hispanic or Latino/o or of Spanish origin, not reported, unknown), and race (American Indian or Alaska Native, Asian Indian, Black or African American, Chinese, Filipino, Japanese, Korean, Native Hawaiian or Other Pacific Islander, Other Asian, Vietnamese, White, Other). Additional listing with demographic data for screen failure subjects will be created.

4.5.2. Baseline Disease Characteristics

Baseline disease characteristics will include:

1) History of cardiovascular risk factors:
    - any risk factor,
    - smoking,
    - hypertension,
    - dyslipidaemia,
    - diabetes mellitus,
    - atrial fibrillation,
    - myocardial infarction,
    - angina pectoris,
    - stroke,
    - coronary revascularization,
    - chronic kidney disease.
2) Index hospitalisation information (screening acute heart failure):
    - aetiology (ischaemic, non-ischaemic, unknown; if non-ischaemic, hypertensive, valvular, idiopathic, congenital, other),
    - AHF duration (newly diagnosed at Index hospitalisation, known documented HF prior to Index hospitalisation),
    - time since initial diagnosis to screening (years) as a continuous variable only for those with known HF prior to Index hospitalisation,
    - acute heart failure in the previous 12 months prior to Index hospitalisation (Yes/No),
    - number of hospitalisations in the 12 months prior to screening (for subjects with at least one previous hospitalisation before screening).
3) Symptoms and signs of heart failure at time of Index hospitalisation:
    - dyspnoea on exertion,
    - dyspnoea at rest while sitting,
    - orthopnoea and paroxysmal nocturnal dyspnoea,
    - peripheral oedema,
    - pulmonary congestion (crackles, rales),
    - liver enlargement,
    - presence of a third heart sound (S3 gallop),
    - jugular venous distension,
    - jugular venous measurement (cm).

4) Other baseline disease characteristics:
    - left ventricular ejection fraction (%), left ventricular ejection fraction as categorical variable (<40%, 40-<50%, >=50%)
    - New York Heart Association Classification (Class I, II, III, IV),
    - baseline weight (kg), height (cm), BMI (kg/m^2) and temperature (°C),
    - baseline laboratory data: haemoglobin (g/dL), haemoglobin as categorical variable (<10, 10-14, >14), anaemic/non-anaemic subjects (anaemic: adult males with Hb < 13 g/dL, adult females, non-pregnant with Hb <12), serum ferritin (ng/mL), serum ferritin as categorical variable (<100, 100-<300, >=300 ng/mL), transferrin saturation (%), transferrin saturation as categorical variable (<20%, >=20%), phosphorus (mg/dL), phosphorus as categorical variable (<1, 1-<2, 2-<2.5, 2.5-<4.5, >=4.5), creatinine (mg/dL), Brain natriuretic peptide (BNP) (pg/mL), N-terminal-probrain natriuretic peptide (NTproBNP) (pg/mL).
    - medical history information (Percutaneous coronary intervention [PCI], Coronary artery bypass surgery [CABG], Implantable cardioverter defibrillator [ICD], Cardiac resynchronization therapy [CRT]) based on prior procedures.

5) Randomisation factors at the time of randomisation:
    - sex, age (<70 years/≥70 years),
    - HF aetiology (ischaemic/non-ischaemic/unknown),
    - HF duration (newly diagnosed at Index hospitalisation/known documented HF prior to Index hospitalisation),
    - country.

    Note: these will be summarised based on the randomisation file and not based on eCRF data that could have been updated after the randomisation by minimisation.

4.5.3. Medical History

Medical history will be coded using MedDRA and summarized by SOC and PT, presenting numbers and percentages of subjects with each reported history. Medical history will also be listed.

4.5.4. Prior Medications

See section 4.8.8.

4.5.5. Prior Procedures

See section 4.8.9.

4.6. Efficacy Evaluation

The analysis of the primary, secondary and other outcomes described below will be performed on the FAS. Sensitivity analyses will be performed on the PP analysis set.

Due to the Covid-19 pandemic, a sensitivity analyses will be performed for the primary and secondary endpoints on the FAS censoring subjects at index date. The index date is given for each country in the table below and corresponds with the first reported Covid-19 patient in the country. All events after the index date will be excluded and subject's follow-up time will be considered only up to the index date.

Table 4 Index Dates

Country	Index Date
Argentina	02-Mar-2020
Brazil	24-Feb-2020
Croatia	24-Feb-2020
Georgia	25-Feb-2020
Israel	20-Feb-2020
Italy	29-Jan-2020
Lebanon	20-Feb-2020
Netherlands	26-Feb-2020
Poland	03-Mar-2020
Romania	25-Feb-2020
Singapore	22-Jan-2020
Spain	30-Jan-2020
Sweden[1]	NA
United Kingdom[1]	NA
Ukraine	02-Mar-2020

[1] No active subject after the index date in this country.

All inpatient hospitalisations, all urgent heart failure visits, and all deaths will be reviewed by the Clinical Endpoint Committee (CEC) to determine whether they are CV-related or not. CV hospitalisations and urgent heart failure visits will be further adjudicated as due to worsening HF, myocardial infarction, unstable angina, and other CV event.

A death with a cause classified by the adjudication committee as "unknown" will be considered as a cardiovascular death. A death with a cause classified by the adjudication committee as "undetermined" will be considered as a non-cardiovascular death. For all other cases, the final adjudicated classification will be taken into consideration for the analyses described below.

Incomplete hospitalisation dates will be imputed in the following way:

Hospitalisation start date:

1. If the start date of a hospitalisation is partially missing and the month and year or the year are equal to those of the randomisation date and the hospitalisation end date is after or equal to the randomisation date or missing, then the hospitalisation start date will be imputed as the randomisation date.

2. If the hospitalisation end date is before the randomisation date, the hospitalisation start date will be imputed as the hospitalisation end date if the month and/or year is the same.

3. If the start date is completely missing, then the start date will be imputed as the hospitalisation end date.

4. Otherwise the month and/or day will be replaced by January and/or 1.

Hospitalisation end date:

1. Incomplete stop dates will be imputed as the last day of the month/year if day/month is missing, or the date of death, whichever is earlier. If imputed end date is after End of Study (see section 4.2.13), End of Study date will be imputed as stop date instead.

2. In all other cases the incomplete stop date will not be imputed.

For all analyses up to 375 days, study day 375 is included. Similarly, for analyses up to day 30, study day 30 is included.

4.6.1. Primary Endpoint

The primary endpoint is the composite of recurrent HF hospitalisations and CV death up to 52 weeks after randomisation, as confirmed by the CEC. If a subject is hospitalised due to HF and dies on the same day from any CV event, this would be counted as one event. All events up to the last known date or study day 375, whichever occurs first, will be considered for this endpoint.

The HF hospitalisation and CV death rates per 100 subject-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 subject-years of time on study (see section 4.2.14) of all subjects in each treatment group multiplied by 100.

Descriptive statistics will provide, per treatment group, the total number of events (HF hospitalisation and CV death), the number (%) of subjects with at least one event, and the number (%) of subjects with more than one event. The number of HF hospitalisations and CV deaths per subject and the time on study will be summarized as continuous and categorical variables. The HF hospitalisation and CV death rates per 100 subject-years will be reported by treatment group. The rate ratio (95% confidence interval [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 risk of repeat hospitalisation [7]; this overdispersion parameter will be the same across the treatment groups and randomisation strata. Varying follow-up times between the patients will be accounted for by including log-transformed time on study of each subject in years as intercept.

The negative binomial model will be adjusted for the following baseline covariates as measured at time of randomisation: sex, age at randomisation, HF aetiology (ischaemic/non-ischaemic/unknown), HF duration, and country. If there are too few subjects in some countries, country can be replaced for the adjustment by region as described in section 4.5.1. A sensitivity analysis will be performed using an unadjusted model.

SAS code to be used:

```
proc genmod data=dataset;
       class armcd (ref='placebo') sex hf_aetio hf_duration country;
       model count = armcd sex age hf_aetio hf_duration country / offset=logfu_dur
link=log dist=negbin type3;
       lsmeans armcd / exp cl diff;
       ods output lsmeans=lsm;
       ods output parameterestimates=est;

      *** Trt Comparison estimates;
       estimate 'Treated vs. placebo' armcd  1 -1 /exp alpha=0.05  ;

run;
```

logfu_duration is the log-transformed time on study of each subject in years.

Statistics will include the estimated rate of events per year, with 95% CI, per treatment group, and the estimated rate ratio between treatment groups, with 95% CI and p-value.

A descriptive graphical representation of the cumulative risk ratio (FCM vs placebo) over time will also be provided based on the calculated cumulative rate of events per 100 subjects over time in each treatment group.

Additionally, as the analysis of HF hospitalisations could be confounded by the competing risk of death, a confirmatory analysis will be performed on the FAS using the joint frailty model in order to analyse repeat hospitalisation data whilst accounting for the associated mortality rate [8]. The joint model allows for the modelling of the recurrent events and time to death simultaneously, including a common frailty term. This joint frailty model will give an estimate for the recurrent HF hospitalisation rate ratio which takes into account CV death as informative censoring and an estimate for the hazard ratio for CV death which takes into account the effect of recurrent hospitalisation on death. Both rates will be displayed with 95% CIs and p-values. For this analysis, if both a hospitalisation and a death occur on the same day, only the death will be counted.

The recurrent event process can be modelled by a random effects (frailty) proportional hazards model. In the presence of a dependent terminal event, the random effects are also incorporated into the model for the terminal events. The SAS code for this analysis will be based on [9]. General steps are described below:

- Generate a dataset with one row for each type of event including the following variables:
  - unique subject ID (*usubjid*),
  - covariates: categorical variables split in binary dummy variables,
  - treatment groups (*trt*): 1 for IV FCM and 0 for placebo
  - time to hospitalisation, censor or death (*timevar*), and
  - Event status (*event*): 0 for censoring, 1 for hospitalisation (recurrent event), and 2 for death (terminal event).

  Note: the dataset may include several rows for the same subject. All subjects have to have a row with either censoring or death.
  Note: the earliest from the hospitalisation start date or emergency start date will be used for time to hospitalisation, when applicable.
  Note: prolonged index hospitalisations will have the start date for this analysis set to randomisation date.
- Calculate the quantiles of *timevar* separately for time to hospitalisation (*event* = 1) and for time to death (*event* = 2). The last interval for recurrent events and for death will then be prolonged up to the last censoring/death date within the dataset.
- Merge with the dataset generated in the first step.
- Calculate the duration and the indicator of event for recurrent event in each quantile interval:
  - For recurrent events, there are 10 variables dur_r$_k$, k = 01, 02, ..., 10 with all zeroes for a row with a recurrent event and with length of follow-up within each interval for a row with censoring or death, and 10 variables event_r$_k$ for the indicator of the recurrent event happening in intervals 1 to 10, respectively;
  - For death, there are 10 variables dur_d$_k$ filled with follow-up time within each interval for censoring or death and with all zeroes for rows with recurrent event. Variable event_d$_k$. takes the value of 1 if the event is death in the interval k, and 0 otherwise.

- Specify the initial values of the parameters in dataset INPAR. The piecewise constant baseline hazards are denoted by r_{01}, r_{02}, ..., r_{10} for recurrent events, and h_{01}, h_{02}, …, , h_{10} for terminal event.
- Use the following SAS code to get the parameter estimates. For simplicity, no covariates are included in the code below.

```
ods output ParameterEstimates= PAREST;

proc nlmixed data=all qpoints=x noad;
parms / data=INPAR;
bounds r01 r02 r03 r04 r05 r06 r07 r08 r09 r10 h01 h02 h03 h04 h05 h06
h07 h08 h09 h10 theta >=0;

/* baseline hazard and cum baseline hazard, recurrent events */
base_haz_r=r01*event_r1+r02*event_r2+r03*event_r3+r04* event_r4 +
r05*event_r5+r06*event_r6+r07*event_r7+r08*event_r8
+r09 * event_r9 + r10 * event_r10;

cum_base_haz_r=r01*dur_r1+r02*dur_r2+r03*dur_r3+r04*dur_r4 +
r05*dur_r5+r06*dur_r6+r07*dur_r7+r08*dur_r8+r09*dur_r9 +
r10 * dur_r10;

/* baseline hazard and cumulative baseline hazard for death */

base_haz_d=h01*event_d1+h02*event_d2+h03*event_d3+h04*event_d4 +
h05*event_d5+h06*event_d6+h07*event_d7+h08*event_d8+
h09 * event_d9 + h10 * event_d10;

cum_base_haz_d=h01 * dur_d1 + h02 * dur_d2 + h03 * dur_d3 +
h04 * dur_d4 + h05 * dur_d5 + h06 * dur_d6 + h07 * dur_d7 +
h08* dur_d8 +h09 * dur_d9 + h10 * dur_d10;

mu1= beta1 * trt + nu;/* for recurrent event */
mu2= alpha1 * trt + gamma * nu; /* for death event */
loglik1=-exp(mu1) * cum_base_haz_r;
loglik2=-exp(mu2) * cum_base_haz_d;

/*log likelihood for recurrent event */
if event=1 then loglik=log(base_haz_r) + mu1;

/*log likelihood for death */
if event=2 then loglik=loglik1 +log(base_haz_d)+mu2+loglik2;

/*log likelihood for censoring */
if event=0 then loglik=loglik1 + loglik2;

model timevar ~ general(loglik);
random nu ~ normal(log(1/sqrt(1+theta)),log(1+theta)) subject=usubjid
out=nu_est;
```

```
predict exp(loglik2) out=outs; /*estimated survival function of death event*/
predict loglik1 out=cumh; /*estimated cum hazard of recurrent event*/
run;
```

- Take the natural exponential of the estimates to get the rate ratio and the hazard ratio with corresponding 95% confidence intervals.

In case the joint frailty model adjusted for baseline covariates does not converge, unadjusted model will be used instead.

4.6.2. Secondary and Other Endpoints

The secondary and other endpoints listed below will evaluate the effect of IV FCM relative to placebo. These will be analysed on the FAS and as a sensitivity analysis on the PP set, using adjudicated events based on the final decision of the CEC.

Secondary endpoints:

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

Hochberg's procedure will be used to control the overall Type I error for the evaluation of the secondary endpoints on FAS at the FWER of 5% two-sided. All secondary endpoints will be analysed as described further in this section, p-values will be sorted from the smallest to the largest and compared with Hochberg's critical values (see Table 5). The highest p-value with lower value than the Hochberg's critical value will be chosen. This p-value and all lower p-values will be considered statistically significant at overall level 5% two-sided.

Table 5 Hochberg's Critical Values

Ordered p-values	Hochberg's critical values
$p\text{-value}_1$	0.05/5 = 0.01
$p\text{-value}_2$	0.05/4 = 0.0125
$p\text{-value}_3$	0.05/3 = 0.0166
$p\text{-value}_4$	0.05/2 = 0.025
$p\text{-value}_5$	0.05/1 = 0.05

Other endpoints:

- 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 up to 30 days after randomisation.
- The composite of CV hospitalisations or CV death analysed as time to first event up to 30 days after randomisation.
- HF hospitalisations up to 30 days after randomisation (analysed as a recurrent event).
- HF hospitalisations up to 30 days after randomisation (analysed as time to first event).
- HF hospitalisations up to 52 weeks after randomisation (analysed as time to first event).
- CV hospitalisations up to 30 days after randomisation (analysed as a recurrent event and time to first event).
- CV hospitalisations up to 52 weeks after randomisation (analysed as a recurrent event and time to first event).
- The composite of CV hospitalisations or CV death analysed as time to first event up to 52 weeks after randomisation.
- CV mortality analysed as time to first event up to 30 days after randomisation.
- All-cause mortality analysed as time to first event up to 30 days after randomisation.
- All-cause mortality analysed as time to first event up to 52 weeks after randomisation.
- Proportion of subjects 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 (KCCQ-12) up to 52 weeks after randomisation. *Note: Described in section 4.8.10.*
- Change from baseline in the European Quality of Life – 5 Dimensions questionnaire up to 52 weeks after randomisation. *Note: Described in section 4.8.10*.
- Days lost due to HF hospitalisations or CV death up to 30 days after randomisation.
- In addition, the endpoints using HF and CV hospitalisations will be repeated including urgent heart failure visits (see section 2.5.3)

Recurrent event analysis:
For the recurrent event analysis, descriptive statistics (total number of events, number of subjects with at least one event, number of events per subject, follow-up duration, rate per 100 subject-years) will be provided, and a negative binomial model will be used to estimate the rate ratio between treatment groups as described for the analysis of the primary endpoint (see section 4.6.1for details). The analysis will be done for events occurring within 30 days of randomisation. For hospitalisations, the start date will be used. The analysis will be repeated to include all events happening during the 52 weeks after randomisation, i.e. up to the last known date or study day 375, whichever occurs first.

The joint frailty model will be fitted for the composite endpoints up to week 52 only.

Time to first event analysis:
For the time to first event analysis, the first occurrence of the relevant event will be used. The time to event in days will be defined as date of event – randomisation date + 1, with the date of event being the start date of hospitalisation (the earliest from the hospitalisation start date or emergency start date, when applicable) or date of death as appropriate. Prolonged index hospitalisations will have the start date for time to event analyses set to randomisation date.

For the analysis of events within 30 days after randomisation, only events starting within these 30 days will be taken into account. Subjects with no event at 30 days will be censored at 30 days or last known date, whichever comes first. For the analysis of events up to 52 weeks, the first incidence of the relevant event up to the last known date or study day 375, whichever occurs first, will be taken into account. Subjects with no event will be censored at last known date or study day 375, whichever occurs first. In addition, a sensitivity analysis will be performed looking at events up to last available value (see section 4.2.16).

The probability of subjects having an event will be displayed by treatment group in the form of cumulative probability curves estimated using the non-parametric Kaplan-Meier method. Point estimates and corresponding 2-sided 95% CIs using the Greenwood's variance estimator will be provided at each scheduled visit (i.e., Weeks 6, 12, 24, and 52). Percentiles (25th, 50th, and 75th) and corresponding 2-sided 95% CIs will also be provided; any of the percentiles not reached will be presented as N/A. Survival estimates at each time point where any patient had event or was censored will be also displayed.

The number of subjects with at least 1 event and the event hazard rate per 100 subject-years "at risk" (estimated as the number of subjects with at least 1 event divided by the subject-years at risk of event) will be displayed by treatment group. Subject-years at risk of event will be taken as the sum of the observation time from start of study drug until the first occurrence of the event concerned, or until censoring. The hazard ratio (relative to placebo), its 95% CI and the associated p-value will be provided using Cox proportional hazards regression.

SAS code for time to event Cox regression (code may be updated to fit the data)

Assume the response variable, time to first event, is TFE and the censored status variable is EVENT (0=censored observation; 1=event observation).

The option 'rl' in the model statement produces 95% CI for the hazard ratio.

```
PROC PHREG DATA=dataset ;
       CLASS armcd(ref='Placebo') sex hf_aetio hf_duration country /param=glm;
       MODEL tfe*event(0)= armcd sex age hf_aetio hf_duration country
                  / risklimits type3;
       contrast "IV FCM. vs Placebo"  armcd 1 -1 /estimate=exp;
       ods output parameterestimates=parmest;
            ods output ContrastEstimate=ContrastEstimate;
RUN;
```

NYHA functional class:

NYHA functional class is assessed at 6, 12, 24, and 52 weeks after randomisation as classes I, II, III, and IV. If a subject dies, then class V will be added for all remaining visits. If subject is hospitalised at any point during any post-baseline visit and this subject does not have any NYHA assessment for this visit (including imputed class V if subject dies), then class IV is imputed for such visit. For change from baseline categories, differences between actual classes will be calculated. The NYHA class will be analysed using a repeated measurement analysis of the ordered polytomous response, adjusted for treatment, time, and baseline NYHA class as well as minimization factors. The generalized estimating equations (GEE) method introduced by Liang and Zeger [10] will be used. This method uses marginal modelling of ordinal response, and it is appropriate when the regression parameters are the interest rather than the variance-covariance structure of the longitudinal data.

Similar sensitivity analyses will be performed without the imputation for subjects who die or are hospitalised.

A shift table presenting change in categories of NYHA from baseline to each visit and last available value will be provided (with imputation).

SAS code (code may be updated to fit the data)

scorechg_NYHA has values of 1, 2, 3, 4 for classes I, II, III and IV, respectively at 6, 12, 24, and 52 weeks. The model allows for missing values. Base corresponds to the baseline NYHA functional class.

```
proc genmod data=dataset rorder=internal  ;
      class armcd (ref=="Placebo") visit usubjid base sex hf_aetio hf_duration
country;
      model score_NYHA = armcd visit base sex age hf_aetio hf_duration country /
dist=multinomial link=cumlogit;
      repeated subject=usubjid/ type=IND;
      estimate 'OR' armcd 1 -1 / exp;
run;
```

Note: baseline included in the model. The odds ratio resulting from the ESTIMATE Statement Results indicates that the odds of IV FCM being in lower response categories is "X.XX" times the odds of Placebo being in lower response categories. Lower response categories are better for score_NYHA.

sources: http://support.sas.com/resources/papers/proceedings16/11702-2016.pdf;

Number of days lost due to HF hospitalisation or CV death:
The number of days lost due to HF hospitalisation within 30 days after randomisation and within 52 weeks after randomisation (up to the last known date or study day 375, whichever occurs first) will be calculated for each subject as the total number of days of HF hospitalisation (confirmed as being due to HF by CEC decision), excluding the index hospitalisation. Prolonged index hospitalisations will have the start date set to randomisation date and number of days lost will be computed from this day. The days lost due to CV death will be added to the number of days lost due to HF hospitalisation. This number of days will be summarised as a continuous variable by treatment group.

A negative binomial model similar to the one described in section 4.6.1 will be fitted on the number of days lost due to HF hospitalisation or CV death, with the log-transformed time on study of each subject in years as an offset.

Proportion of subjects with an event

An overall summary table presenting the number and proportion of subjects with an event (HF hospitalisations, CV hospitalisations, CV mortality; composite and individual categories) within 30 days of randomisation, within 52 weeks after randomisation (up to the last known date or study day 375, whichever occurs first) will also be presented. The following categories will be presented:

- Subjects with at least one HF hospitalisation (excluding and including urgent HF visits).
- Subjects with at least one CV hospitalisation.
- Subjects with CV death.
- Subjects with at least one HF hospitalisation (excluding and including urgent HF visits) or CV death.
- Subjects with at least one CV hospitalisation or CV death.

The p-value from Fisher's exact test will be used to compare the treatment groups. The proportions of subjects with an event will be compared using Fisher's exact test. In addition, the 95% confidence interval for the proportion using exact (Clopper-Pearson) estimates will be provided.

4.6.3. Exploratory

Exploratory analyses of primary and secondary endpoints will be performed for the subgroups defined in section 4.2.6, on the Full Analysis Set, provided that enough subjects are included in each subgroup category for the model to converge.

Primary Endpoint Exploratory Analyses

Descriptive statistics per subgroup and treatment group will be presented and will include the total number of events (HF hospitalisation and CV death), the number (%) of subjects with at least one event, the number (%) of subjects with more than one event, the time on study, and the HF hospitalisation and CV death rates per 100 subject-years.

The negative binomial model described in section 4.6.1 will be repeated including each of the subgroup variable as covariate and an interaction effect between the subgroup variable and the treatment group (one model for each subgroup). The estimated rate of events per 100 subject-years will be presented by subgroup and treatment group with the 95% CI. The estimated rate ratio (95% CI and p-value) between treatment groups for each subgroup with be presented as well as the overall p-value for the interaction. The model will be performed both with and without adjustment for randomisation factors.

For the following subgroups (randomisation factors), the subgroup covariate will be included only once in the model:

- Sex
- Ischaemic Aetiology of HF (ischaemic, non-ischaemic)
- Diagnosis of Heart Failure (newly diagnosed at index hospitalisation versus known documented HF prior index hospitalisation).

For analysis of subgroup by age, the age covariate will be removed from the model and the factor age (by tertiles) will be included instead.

A forest plot of rate ratios from the main analysis and from all different subgroups will be provided.

SAS Code for negative binomial model with subgroup interaction (code may be updated to fit the data):

```
proc genmod data=dataset;
       class armcd (ref='placebo') sex hf_aetio hf_duration country subgrp (ref='2');
       model count = armcd sex age hf_aetio hf_duration country subgrp armcd*subgrp  /
offset=logfu_dur link=log dist=negbin type3;
       lsmeans armcd armcd*subgrp  / exp cl diff e;
       ods output lsmeans=lsm;
       ods output estimates=estimates;
       ods output modelanova=type3;

       * Trt comparison ;
       estimate 'Treated vs. placebo gr1' armcd  1 -1 armcd*subgrp 1 0  -1 0 /exp
alpha=0.05;
       estimate 'Treated vs. placebo gr2' armcd  1 -1 armcd*subgrp 0 1  0 -1 /exp
alpha=0.05;

   /* Subgroup with 3 categories;
   * Trt comparison;
   estimate 'Treated vs. placebo gr1' armcd  1 -1 armcd*subgrp 0 0 1 0 0 -1 /exp
alpha=0.05;
   estimate 'Treated vs. placebo gr2' armcd  1 -1 armcd*subgrp 1 0 0 -1 0 0 /exp
alpha=0.05;
   estimate 'Treated vs. placebo gr3' armcd  1 -1 armcd*subgrp 0 1 0 0 -1 0 /exp
alpha=0.05;
       run;
```

logfu_duration is the log-transformed time on study of each subject in years.

Secondary Endpoints Exploratory Analysis: Recurrent event analysis

The recurrent event analysis similar to primary endpoint analysis will be repeated by subgroup on all subgroups defined in section 4.2.6 for the following endpoints:

- The composite of recurrent CV hospitalisations or CV death up to 52 weeks after randomisation.
- HF hospitalisations up to 52 weeks after randomisation (analysed as a recurrent event)

Secondary Endpoints Exploratory Analysis: Time to first event analysis

The time to first event analysis described in section 4.6.2 will be repeated for each subgroup defined in section 4.2.6 on the following secondary endpoints:

1. CV mortality analysed as time to first event up to 52 weeks after randomisation.
2. The composite of HF hospitalisations or CV death analysed as time to first event up to 52 weeks after randomisation.

The Cox regression will include the subgroup variable and the interaction between treatment and subgroup effect as a covariate. Hazard ratios, 95% CI and the associated p-value by subgroup will be presented, as well as the p-value of global effect of interaction between treatment and subgroup.

For analyses by subgroup of randomisation factors, the subgroup covariate will be included only once in the model as described earlier. A forest plot of hazard ratios from the main analysis and from all different subgroups will be provided.

SAS Code to be used for time to event Cox proportional hazards regression with subgroup interaction (code may be updated to fit the data):

```
PROC PHREG DATA=test2 ;
       CLASS armcd(ref='Placebo') sex subgrp (ref='2') /param=glm;
       MODEL tfe*event(0)= armcd sex subgrp armcd*subgrp / risklimits type3 rl;
       *hazardratio armcd / at (subgrp=all) cl=wald ;
       contrast "IV FCM. vs Placebo gr1"  armcd 1 -1 subgrp 0 armcd*subgrp 1 0 -1 0
/estimate=exp;
       contrast "IV FCM. vs Placebo gr2"  armcd 1 -1 subgrp 0 armcd*subgrp 0 1 0 -1
/estimate=exp;

   /* Subgroup with 3 categories;
   contrast "IV FCM. vs Placebo gr1"  armcd 1 -1 subgrp 0 armcd*subgrp 0 0 1 0 0 -1
/estimate=exp;
   contrast "IV FCM. vs Placebo gr2"  armcd 1 -1 subgrp 0 armcd*subgrp 1 0 0 -1 0 0
/estimate=exp;
   contrast "IV FCM. vs Placebo gr3"  armcd 1 -1 subgrp 0 armcd*subgrp 0 1 0 0 -1 0
/estimate=exp; */

       ods output ContrastEstimate=ContrastEstimate;
       *ods output HazardRatios=hr ;
       *ods output parameterestimates=parmest;
       ods output modelanova=modelanova;
RUN;
```

Secondary Endpoint exploratory analysis: Number of days lost due to HF hospitalisations or CV death

The number of days lost due to HF hospitalisations or CV death up to 52 weeks after randomisation analysis will be repeated by subgroup for each subgroup defined in section 4.2.6.

A forest plot of ratio ratios from the main analysis and from all different subgroups will be provided.

NYHA functional class exploratory analysis:

NYHA functional class analysis described in section 4.6.2 will be performed by subgroup (see section 4.2.6). The ordered polytomous response model will include the subgroup variable and interaction between treatment and subgroup as covariate. Odd-ratio by subgroup will be provided. For analyses by subgroup of randomisation factors, the subgroup covariate will be included only once in the model. For analysis of subgroup by age, age covariate will be removed from the model and the factor age by tertiles will be included instead. For subgroup of NYHA class, the analysis will be performed on the subset of subjects with NYHA class II or III at baseline and the baseline NYHA class will be included only once in the model.

A forest plot of odds ratios from the main analysis and from all different subgroups will be provided.

SAS Code to be used for subgroup analysis (code may be updated to fit the data):

```
proc genmod data=dataset rorder=internal  ;
      class armcd (ref='Placebo') visit usubjid base sex hf_aetio hf_duration country
subgrp (ref='1') ;
      model score_NYHA = armcd visit base sex age hf_aetio hf_duration country subgrp
armcd*subgrp / dist=multinomial link=cumlogit TYPE3 ;
      repeated subject=usubjid/ type=IND;
      estimate 'Log OR Treated vs. placebo gr1' armcd 1 -1 armcd*subgrp 0 1  0 -1  /
exp;
       estimate 'Log OR Treated vs. placebo gr2' armcd 1 -1 armcd*subgrp 1 0  -1 0 /
exp;

  /* Subgroup 3 categories
  estimate 'Log OR Treated vs. placebo gr1' armcd 1 -1 armcd*subgrp 0 0 1  0 0 -1
/exp;
  estimate 'Log OR Treated vs. placebo gr2' armcd 1 -1 armcd*subgrp 1 0 0  -1 0 0
/exp;
  estimate 'Log OR Treated vs. placebo gr3' armcd 1 -1 armcd*subgrp 0 1 0  0 -1 0
/exp;  */
       ods output estimates=estimates ;
       ods output type3=type3 ;
run;
```

Additional exploratory analyses not described above may be performed if indicated by the medical review(s) of the data.

4.7. Pharmacokinetic Evaluations

Not Applicable.

4.8. Safety Analyses

Unless specified otherwise, safety analyses will be conducted using the SAF analysis set, and presented based on actual treatment received.

4.8.1. Treatment Exposure and Compliance

Time on study (follow-up) in weeks and subject-years on study as defined in sections 4.2.14 and 4.2.18 will be summarised as continuous variables. Time on study drug as defined in section 4.2.15 will also be summarised.

Treatment Exposure

The number of injections of study drug per subject will be summarised as a categorical variable (1, 2, 3, 4). The total amount of study drug given and planned (see Table 6 and Table 7) across

visits (mL) will be calculated for each subject, and will be summarised by treatment group. Summary statistics for the doses received (in mL and in mg) at each visit be also presented.

The total amount of study drug and the doses received at each visit in mL and mg will also be summarised as a continuous variable.

Treatment Compliance

The planned dose will be derived based on the protocol number, protocol consent and re-consent dates, serum pregnancy test result, weight, Hb levels, and ID status as per Table 6 and Table 7 below. Table 7 will apply only for subjects who consented to protocol 2 or 3 or if the subject re-consented to protocol 2 and the injection date is on or after the protocol re-consent date. ID is defined as serum ferritin <100 ng/mL, or 100 ng/mL ≤ serum ferritin ≤299 ng/mL if transferrin saturation (TSAT) is <20%. The laboratory and vital sign values closest to the injection date and time (<=) will be used. In case no injection was done, the value closest to the visit date will be used.

For the protocol 1, the first dose of study treatment is administered for all randomised subjects on the same day as randomisation – i.e., at Visit 2 while the subject is still hospitalised for the Index hospitalisation. The subsequent administrations of study treatment are done as part of the outpatient clinic visits at Week 6 (Visit 3), and at Weeks 12 (Visit 4) and 24 (Visit 5) only for subjects in whom ID persists and for whom Hb ≥8 g/dL and ≤15 g/dL. The serum pregnancy test must also be negative for the respective visit for females of childbearing potential.

The dosing regimen for protocol 1.2 is similar to the one from protocol 1 except for the subjects from The Netherlands (NL). For NL subjects, the lower threshold of Hb values is set to 10 g/dL.

For the protocol 2 and 3, dosing at Week 6 (Visit 3) is based on the iron need upon screening Hb and weight values to replete iron as described in Table 7 and only be done in subjects for whom Hb ≤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. The serum pregnancy test must also be negative for the respective visit 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.

Table 6 Study drug Dosing Regimen Protocol 1

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

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

Table 7 Study drug Dosing Regimen Protocols 2, 3

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 algorithm to calculate the planned dose is described in Appendix II.

The calculated planned dose and the dose administered as collected in the eCRF will be used to calculate the dosing information (dose given as planned, reduced, increased). It will be summarised for each treatment visit (Baseline, Visit 3 [Week 6], Visit 4 [Week 12], and Visit 5 [Week 24]).

The total amount of study drug given during the study will be calculated for each subject and will be compared to the amount expected to be given for each subject based on weight, Hb levels, and ID status. Treatment compliance will be calculated for each subject and summarised by treatment group and summarised as continuous and categorical variable (<80, 80-120, > 120 as categories)

- Total amount = total volume administered in mL over all visits.
- Expected amount = total volume in mL that should have been administered as described in Table 6.
- Compliance rate = (total amount/expected amount)*100.

Treatment compliance and drug concentration information will also be reported in data listings.

4.8.2. Adverse Events

Adverse events are to be recorded throughout the study, beginning at the moment of informed consent. AEs will be coded using MedDRA and displayed in tables and listings by SOC and PT.

Analyses of adverse events will be performed for those events that are considered treatment-emergent, where a treatment-emergent AE (TEAE) is defined as one that started, or worsened in severity or seriousness following the first dose of IMP. An AE with onset prior to the start of the administration of the first dose of study drug, or where the stop date is before the start of the administration of the first dose of study drug, or where the study drug injection was not started, will be considered as pre-study. In case the onset date is on the same day as the first dose of study drug and either the time of first dose or time of AE onset is missing, then AE is considered treatment-emergent.

AE intensity will be qualified as mild, moderate, or severe. The relationship to the study drug will be qualified as related (including categories certain, probable/likely, possible) or unrelated.

If the AE start date is missing or partial, the AE will be assigned to the appropriate period using available start date information and the stop date, if present.

Incomplete AE-related dates will be imputed in the following way:

AE start date:

- If the start date of an AE is missing completely, or is partially missing and the month and year or the year are equal to those of the first study drug start date and the AE end date is after or equal to the first study drug start date or missing, then the AE start date will be imputed as the first study drug start date. In case the end date of AE is the same as the IMP start date, non-missing times will also be checked.
- If the AE end date is before the first study drug start date, the AE start date will be imputed as the AE end date if month and/or year is the same.
- Otherwise the month and/or day will be replaced by January and/or 1.

AE end date:

- Incomplete stop dates will be imputed as the last day of the month (if only the day is missing), or the date of death, whichever is earlier.
- In all other cases the incomplete stop date will not be imputed.

Adverse events will be summarised by subject incidence rates, adjusted incidence rates, and number of events. An overview of TEAEs will present the numbers and percentages of subjects experiencing at least one event for the following categories:

- All AEs.
- TEAEs.
- TEAEs by relationship to study drug.
- TEAEs by severity.
- Serious TEAEs.
- Related Serious TEAEs.
- Severe Serious TEAEs.
- TEAEs leading to treatment discontinuation.
- TEAEs leading to study discontinuation.
- All Fatal AEs.
- Fatal TEAEs.
- Related Fatal TEAEs.
- TEAEs leading to hospitalisation.
- TEAEs of clinical interest "CV Death" or "HF Hospitalisation".
- TEAEs of special interest related to study drug.

Additionally, AEs in the categories listed below will also be summarised by incidence rates and adjusted incidence rates by SOC and PT, as well as number of events (Note: in the descriptive analysis for the incidence rate, each subject will contribute only once to the count for a given SOC or Preferred Term, regardless of the number of episodes experienced):

- TEAEs.
- TEAEs related to study drug.
- TEAEs by relationship (without adjusted incidence rates).
- Severe TEAEs.
- TEAEs by severity (without adjusted incidence rates).
- Serious TEAEs.
- Serious TEAEs occurring in > 5 % of the subjects.
- Non-serious TEAEs.
- Serious TEAES related to study drug.
- TEAEs leading to treatment discontinuation, "drug withdrawn" in the eCRF.
- TEAEs leading to study discontinuation.
- Serious TEAEs by severity,
- Fatal TEAEs,
- Fatal TEAEs related to study drug,
- TEAEs of clinical interest (by PT only),
- TEAEs of special interest (by PT only) related to study drug.

Adjusted incidence rate will be calculated by dividing the number of subjects with a particular TEAE by the subject-years of time on study (see section 4.2.14) of all subjects in each treatment group.

In the tabulations by severity or relationship, each subject will contribute only once to each of the incidence rates by using the worst severity/strongest relationship reported within the period of interest; all events experienced will be counted in the event rates.

If the relationship is missing, the AE will be considered related to study drug. If the severity is missing, the AE will be considered to be severe.

Cardiovascular AE terms of clinical interest as reported by Investigators will be listed in this order in the table:

1. CV death
2. HF hospitalisation

The CV AEs of clinical interest as reported by Investigators will be identified as follows:

1. For HF hospitalisations: PT = "Cardiac failure", "Cardiac failure acute", "Cardiac failure congestive". or "Cardiac failure chronic" and led to or prolonged hospitalisation = Yes
2. For CV death: SOC = "Cardiac Disorders" and results in death = Yes, and PT="Sudden cardiac death" in SOC "General disorders and administration site conditions"

AEs of special interest include "hypersensitivity reactions", "hypophosphatemia", "injection/infusion site reactions" and "haemosiderosis". Only events related to study drug are considered. Each category will be identified as follows:

1. Hypersensitivity reactions: PT = "Hypersensitivity", "Anaphylactic reaction", "Anaphylactic shock", "Anaphylactoid shock" or "Anaphylactoid reaction"
2. Hypophosphatemia: PT = "Blood phosphorus decreased", "Blood phosphorus abnormal", "Hypophosphataemia", "Hypophosphataemic osteomalacia" or "Hereditary hypophosphataemic rickets"
3. Injection/infusion site reactions: HLT = "Infusion site reaction", "Injection site reactions", "Administration site reactions NEC" or "Infusion related reaction"
4. Haemosiderosis: PT = "Haemosiderosis", "Haemeatochromatosis", "Iron overload", "Hepatic siderosis", "Cardiac iron overload", "Pulmonary haemosiderosis" or "Superficial siderosis of central nervous system"

A listing of pre-study AEs and listing of AEs starting between randomisation date and start of treatment will be presented. All TEAEs occurring on study will be listed in subject data listings, as will related TEAEs, SAEs, related SAES, TEAEs leading to study drug discontinuation or death. Data will not be imputed in the listings.

Relevant pregnancy information captured in the eCRF will be listed.

All deaths details will be listed.

4.8.3. Special Situations

Special situations collected in the eCRF will be listed.

The following special situations will be reported by category and preferred term:

- Pregnancy or breastfeeding
- Medication abuse
- Medication error
- Medication misuse
- Medication overdose
- Occupational exposure: *defined as 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

4.8.4. Event Adjudication

Details on adjudications performed by the CEC will be tabulated for the SAF analysis set. The number of events adjudicated and the adjudication decisions will be summarised by treatment group, along with the number of hospitalisations adjudicated, the number of urgent HF visits (including emergency room and unscheduled outpatient visits), and the number of deaths adjudicated with cause of death.

Adjudication information will also be listed.

4.8.5. Laboratory Data

Laboratory data, including haemoglobin (g/dL), serum ferritin (ng/mL), transferrin saturation (%), and phosphorus (mg/dL), are assessed at Screening, Week 6, Week 12, Week 24, and Week 52 (except for pregnancy tests). Please see Appendix III for a description of parameter, unit and number of decimals to be displayed in summary tables.

The actual value and change from baseline to each on-study evaluation will be summarised for each parameter at each scheduled visit, as well as for the last available post-baseline value (see section 4.2.16). Determination of baseline for all endpoints is described in section 4.2.12. For all post-baseline time points, the windowing described in section 4.2.9 will be applied.

Categorical shift tables from baseline to all visits will also be presented, showing the numbers of subjects with values outside the normal ranges as reported on the eCRF (categories Normal, Abnormal Non-Clinically Significant, Abnormal Clinically Significant).

Additionally, a shift table from baseline to all visits and to the lowest post-baseline value will be presented for phosphorus. Categories included in this shift table are: < 1 mg/dL, 1-< 2 mg/dL, 2-< 2.5 mg/dL, 2.5-< 4.5 mg/dL and >= 4.5 mg/dL.

The value of eGFR will be computed using CKD-EPI formula:

eGFR (mL/min/1.73m^2) = 141 x min (S_{cr}/κ,1)$^{\alpha}$ x max (S_{cr}/κ,1)$^{-1.209}$ x 0.993^{age} x 1.018 [if female] x 1.159 [if black],

where

S_{cr} is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

age at baseline is used.

All laboratory data including screening laboratory values (creatinine, eGFR, BNP and NT-proBNP) will be provided in data listings.

Pregnancy test results will be reported in a listing only.

4.8.6. Vital Signs

Vital signs include height (cm) (only at baseline), weight (kg), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats/min), pulse (beats/min), and temperature (° C) (only at baseline). They are assessed at Day 0, Week 6, Week 12, Week 24, and Week 52. Please see Appendix III for a description of parameter, unit and number of decimals to be displayed in summary tables.

Actual values and changes from baseline will be summarized at each visit, as done for laboratory data, for each vital sign parameter. Baseline is defined in section 4.2.12. Actual values of weight will also be summarised by category (<70 kg, ≥70 kg) at each visit.

By-subject listings of vital signs measurements will be presented.

4.8.7. Electrocardiogram

Shifts from baseline to Week 52 or early termination visit and last available post-baseline value relative to the Overall interpretation categories Normal, Abnormal Non-Clinically Significant, and Abnormal Clinically Significant will be tabulated.

The number and percentages of subjects meeting the ICH E14 criteria [2] will also be described. All post-baseline QT, QTcB and QTcF interval values (including unscheduled) will be used.

Absolute QTc interval prolongation:

- QTc interval > 450
- QTc interval > 480
- QTc interval > 500

ECG data for each subject will be provided in data listings, including the finding description.

4.8.8. Concomitant Medications

For analysis, concomitant medications are defined as any medications other than IMP, which are taken any time on or after the date of the first IMP dose. Medications with a start or stop date on or after the first IMP dosing date will be considered concomitant medications. All medications categorised as ongoing at baseline will be considered concomitant medications. Newly started medications are defined as any medications other than IMP, which have an onset on or after the first IMP dose.

Prior medications are defined any medications which are taken any time prior to the first IMP dose (onset before first IMP dose).

Incomplete medication-related dates will be imputed temporarily in the following way in order to assign the medication to the appropriate categories

Medication start date:

- If the start date and end date of medication are missing completely then the medication start date will be imputed as the study drug start date.
- If the start date of a medication is missing completely, or is partially missing and the month and year or the year are equal to those of the first study drug start date and the medication end date is after or equal to the first study drug start date, then the medication start date will be imputed as the first study drug start date.
- If the medication end date is before the first study drug start date, the medication start date will be imputed as the medication end date if month and/or year is the same.
- Otherwise the month and/or day will be replaced by January and/or 1.

Medication end date:

- Incomplete end dates will be imputed as the last day of the month (if only the day is missing) or last day of the last month of the year (if day and month are missing) or the date of death, whichever is earlier.
- In all other cases the incomplete stop date will not be imputed and the stop date will be assumed to be missing.

All medications will be categorized according to a standard dictionary (World Health Organization [WHO] Drug Classification). Counts and percentages of subjects using each medication will be computed and summarized by treatment group, by Anatomical Therapeutic Chemical (ATC) level 2 and level 4 codes and Preferred Name; separate summaries will be prepared for prior, concomitant, and newly started medications. A subject will be counted only once per drug category even if more than one medication is used or the medication is reported more than once.

In addition, a table will be created containing a number of subjects with at least one medication in following categories: ACE inhibitors, Angiotensin II receptor blockers (ARB), Sacubitril-Valsartan (ARNI), Aldosterone Antagonists, Beta-blocking agents, Digitalis glycosides, Loop diuretics, Thiazide and thiazide-like diuretics, Ivabradine, Statin, Acetsalicyl acid, Other antiplatelet drugs, Vitamin K antagonists, Direct thrombin inhibitors, Direct factor Xa inhibitors. Medications included in each category are listed in Appendix IV. The categories are defined by ATC levels 3, 4 and 5, as ATC level 5 is not available for this study, Sponsor's representative will review all medications and categories defined by ATC level 5 will be based on this review. This summary will be done for prior and concomitant medications.

The use of prior, concomitant, and newly started medications will be included in a by-subject data listing. The listing will identify which medications are prior and which are concomitant.

4.8.9. Concomitant Procedures

Pacemakers and other therapies of interest will be identified by a Sponsor's representative and assigned to categories (PCI, CBAG, ICD, and CRT). These prior procedures will be summarized together with other baseline characteristics.

Prior and concomitant procedures collected in the eCRF will be included in a by-subject data listing. The listing will identify which procedures are prior and which are concomitant.

4.8.10. Quality of Life

Quality of life will be assessed using the Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12), the European QoL-5 Dimensions (EQ-5D) questionnaire and the Visual analogue scale for Health State, for the FAS and as a sensitivity analysis for the PP set.

The KCCQ-12 is a health-related quality of life questionnaire for heart failure. It is a 12-item questionnaire that quantifies physical function, symptoms (frequency, severity, and recent change), social function, self-efficacy and knowledge, and QoL. KCCQ-12 is assessed at Day 0 (V2), at Week 2 and Week 4, Week 6 (V3), Week 12 (V4), Week 24 (V5), Week 36 (telephone contact 3), and Week 52 (V6). The KCCQ-12 questionnaire is completed before any trial related procedure performed for the visit concerned. For the telephone contacts, subjects complete the self-administered KCCQ-12 questionnaire at home on the same day as the telephone contact. For each time point, an overall score will be calculated from the scores of the different domains. The UK scoring method will be used as described in Appendix V. The overall summary score and the clinical summary score will be summarised at each visit.

The EQ-5D is a quality of life questionnaire including 5 items/dimensions (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), which will be coded from 1 (best state) to 5 (worst state), and a visual analogue scale (VAS; 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 EQ-5D is assessed at Day 0 (V2), Week 6 (V3), Week 24 (V5), and Week 52 (V6). An index value will be calculated from these results at each visit (see Appendix VI). For each dimension, the number and percentage of subjects reporting each level will be presented. The VAS result and the change from baseline in VAS will be described as continuous variables at each visit.

Additionally, for each questionnaire, the actual values and change from baseline in overall summary score, clinical summary score and physical limitation score (not part of the main set of outputs) will be descriptively summarized at each visit. Treatment difference in KCCQ-12 scores (one model for each score) at Week 2, Week 4, Week 6, Week 12, Week 24, Week 36, and Week 52 will be analysed by comparing the model-adjusted means of the respective visits based on a repeated-measures model including terms for treatment, baseline, time, and treatment-by-time interaction with an unstructured covariance matrix to model the within-subject variability. Treatment difference in EQ-5D index score will be analysed in the same manner for the data collected at Week 6, Week 24, and Week 52.

SAS code to be used:

```
PROC MIXED DATA=dataset order = internal;
CLASS usubjid time treatment sex hf_aetio hf_duration country;
MODEL change=base treatment time treatment*time sex age hf_aetio hf_duration country
/ddfm=kenwardroger;
REPEATED time / subject=usubjid type=un;
LSMEANS treatment *time / pdiff cl at means;
RUN;
```

Number and percentage of subjects with improvement of ≥ 5 points, improvement of ≥ 8 points and deterioration of ≥ 5 points will be presented for KCCQ-12 overall summary score, clinical summary score and physical limitation score at Week 2, Week 4, Week 6, Week 12, Week 24, Week 36 and Week 52. Odds ratio for FCM vs placebo will be presented as well. This analysis will not be part of the main set of outputs.

Results from quality of life questionnaires will be reported in data listings, with details by question and by visit.

4.8.11. Biomarkers

It is planned to perform biomarker analyses in blood samples from approximately 60% of randomised subjects at Day 0, Week 6, Week 25, and Week 52. Analyses of biomarkers will be detailed in a separate biomarker SAP.

5. CHANGES TO PLANNED ANALYSES

Stratification factor age was used as a categorical variable for randomisation. For adjustments by covariates age will be used as a continuous variable for better precision.

6. REFERENCES

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7. CLINICAL STUDY REPORT APPENDICES

7.1. Statistical Tables/Listings and Figures to be Generated

Type*	Section	Title
T	14.1 Disposition/Demographics/Other Characteristics	14.1.1.1 Number of Subjects Randomised by Country, Site and Treatment Group – All Randomised Set
		14.1.1.2 Subject Enrolment – Screened Population
		14.1.1.3 Subject Disposition – All Randomised Set
		14.1.1.4 Subject Populations – All Randomised Set
		14.1.1.5 Overview of Visits - All Randomised Set
		14.1.2.1 Demographics - Full Analysis Set
		14.1.2.2 Demographics - Per Protocol Set
		14.1.2.3 Demographics - Safety Analysis Set
		14.1.3.1 History of Cardiovascular Risk Factors - Full Analysis Set
		14.1.3.2 History of Cardiovascular Risk Factors - Per Protocol Set
		14.1.3.3 History of Cardiovascular Risk Factors - Safety Analysis Set
		14.1.4.1 Baseline Acute Heart Failure Characteristics - Full Analysis Set
		14.1.4.2 Baseline Acute Heart Failure Characteristics - Per Protocol Set
		14.1.4.3 Baseline Acute Heart Failure Characteristics - Safety Analysis Set
		14.1.5.1 Heart Failure Signs and Symptoms - Full Analysis Set
		14.1.5.2 Heart Failure Signs and Symptoms – Per Protocol Set
		14.1.5.3 Heart Failure Signs and Symptoms - Safety Analysis Set
		14.1.6.1 Other Baseline Characteristics - Full Analysis Set
		14.1.6.2 Other Baseline Characteristics – Per Protocol Set
		14.1.6.3 Other Baseline Characteristics - Safety Analysis Set
		14.1.7.1 Randomisation Factors for Minimisation - Full Analysis Set
		14.1.7.2 Randomisation Factors for Minimisation - Per Protocol Set
		14.1.7.3 Randomisation Factors for Minimisation - Safety Analysis Set
		14.1.8.1 Other General Medical History - Full Analysis Set
		14.1.8.2 Other General Medical History – Per Protocol Set
		14.1.8.3 Other General Medical History - Safety Analysis Set
		14.1.9.1.1.1 Prior Medications by ATC Level 2, ATC Level 4 and Preferred Name – Full Analysis Set
		14.1.9.1.1.2 Prior Medications by ATC Level 2, ATC Level 4 and Preferred Name – Safety Analysis Set
		14.1.9.1.2.1 Prior Medications of Special Interest – Full Analysis Set
		14.1.9.1.2.2 Prior Medications of Special Interest – Safety Analysis Set
		14.1.9.2.1.1 Concomitant Medications by ATC Level 2, ATC Level 4 and Preferred Name – Full Analysis Set
		14.1.9.2.1.2 Concomitant Medications by ATC Level 2, ATC Level 4 and Preferred Name – Safety Analysis Set
		14.1.9.2.2.1 Concomitant Medications of Special Interest – Full Analysis Set
		14.1.9.2.2.2 Concomitant Medications of Special Interest – Safety Analysis Set
		14.1.9.3.1 Newly Started Medications by ATC Level 2, ATC Level 4 and Preferred Name – Full Analysis Set

Type*	Section	Title
		14.1.9.3.2 Newly Started Medications by ATC Level 2, ATC Level 4 and Preferred Name – Safety Analysis Set
		14.1.10.1 Exposure and Compliance - Safety Analysis Set
		14.1.10.2 Exposure and Compliance by Visit - Safety Analysis Set
T	14.2 Efficacy	14.2.1.1.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.1.1.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation (Confirmatory Analysis) – Full Analysis Set
		14.2.1.2.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Per Protocol Set
		14.2.1.2.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation (Confirmatory Analysis) – Per Protocol Set
		14.2.1.3.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation (Covid-19 Sensitivity Analysis) – Full Analysis Set
		14.2.1.3.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation (Covid-19 Sensitivity Analysis, Confirmatory Analysis) – Full Analysis Set
		14.2.2 Analysis of Secondary Endpoints (Hochberg's Critical Values)
		14.2.2.1.1.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.2.1.1.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation (Confirmatory Analysis) – Full Analysis Set
		14.2.2.1.2.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Per Protocol Set
		14.2.2.1.2.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation (Confirmatory Analysis) – Per Protocol Set
		14.2.2.1.3.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation (Covid-19 Sensitivity Analysis) – Full Analysis Set
		14.2.2.1.3.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation (Covid-19 Sensitivity Analysis, Confirmatory Analysis) – Full Analysis Set
		14.2.2.2.1.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.2.2.1.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation (Confirmatory Analysis) – Full Analysis Set
		14.2.2.2.2.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Per Protocol Set
		14.2.2.2.2.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation (Confirmatory Analysis) – Per Protocol Set
		14.2.2.2.3.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation (Covid-19 Sensitivity Analysis) – Full Analysis Set
		14.2.2.2.3.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation (Covid-19 Sensitivity Analysis, Confirmatory Analysis) – Full Analysis Set

Type*	Section	Title
		14.2.2.3.1.1 Time to CV Death up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.2.3.1.2 Time to CV Death up to 52 Weeks after Randomisation (Survival Estimates) – Full Analysis Set
		14.2.2.3.2.1 Time to CV Death up to 52 Weeks after Randomisation – Per Protocol Set
		14.2.2.3.2.2 Time to CV Death up to 52 Weeks after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.3.3.1 Time to CV Death up to 52 Weeks after Randomisation (Covid-19 Sensitivity Analysis) – Full Analysis Set
		14.2.2.3.3.2 Time to CV Death up to 52 Weeks after Randomisation (Covid-19 Sensitivity Analysis, Survival Estimates) – Full Analysis Set
		14.2.2.4.1.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.2.4.1.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation (Survival Estimates) – Full Analysis Set
		14.2.2.4.2.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Per Protocol Set
		14.2.2.4.2.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.4.3.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation (Covid-19 Sensitivity Analysis) – Full Analysis Set
		14.2.2.4.3.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation (Covid-19 Sensitivity Analysis, Survival Estimates) – Full Analysis Set
		14.2.2.5.1.1 Number of Days Lost Due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation - Full Analysis Set
		14.2.2.5.1.2 Number of Days Lost Due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation (Confirmatory Analysis) - Full Analysis Set
		14.2.2.5.2.1 Number of Days Lost Due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation - Per Protocol Set
		14.2.2.5.2.2 Number of Days Lost Due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation (Confirmatory Analysis) - Per Protocol Set
		14.2.2.5.3.1 Number of Days Lost Due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation (Covid-19 Sensitivity Analysis) - Full Analysis Set
		14.2.2.5.3.2 Number of Days Lost Due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation (Covid-19 Sensitivity Analysis, Confirmatory Analysis) - Full Analysis Set

Type*	Section	Title
		14.2.2.6.1.1 Recurrent HF Hospitalisations (including urgent HF visits) and CV Death up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.2.6.1.2 Recurrent HF Hospitalisations (including urgent HF visits) and CV Death up to 52 Weeks after Randomisation (Confirmatory Analysis) – Full Analysis Set
		14.2.2.6.2.1 Recurrent HF Hospitalisations (including urgent HF visits) and CV Death up to 52 Weeks after Randomisation – Per Protocol Set
		14.2.2.6.2.2 Recurrent HF Hospitalisations (including urgent HF visits) and CV Death up to 52 Weeks after Randomisation (Confirmatory Analysis) – Per Protocol Set
		14.2.2.7.1.1 Recurrent HF Hospitalisations (including urgent HF visits) up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.2.7.1.2 Recurrent HF Hospitalisations (including urgent HF visits) up to 52 Weeks after Randomisation (Confirmatory Analysis) – Full Analysis Set
		14.2.2.7.2.1 Recurrent HF Hospitalisations (including urgent HF visits) up to 52 Weeks after Randomisation – Per Protocol Set
		14.2.2.7.2.2 Recurrent HF Hospitalisations (including urgent HF visits) up to 52 Weeks after Randomisation (Confirmatory Analysis) – Per Protocol Set
		14.2.2.8.1.1 Time to First Event: Composite of HF Hospitalisations (including urgent HF visits) or CV Death up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.2.8.1.2 Time to First Event: Composite of HF Hospitalisations (including urgent HF visits) or CV Death up to 52 Weeks after Randomisation (Survival Estimates) – Full Analysis Set
		14.2.2.8.2.1 Time to First Event: Composite of HF Hospitalisations (including urgent HF visits) or CV Death up to 52 Weeks after Randomisation – Per Protocol Set
		14.2.2.8.2.2 Time to First Event: Composite of HF Hospitalisations (including urgent HF visits) or CV Death up to 52 Weeks after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.9.1.1 Number of Days Lost due to HF Hospitalisations (including urgent HF visits) or CV Death up to 52 Weeks after Randomisation - Full Analysis Set
		14.2.2.9.1.2 Number of Days Lost due to HF Hospitalisations (including urgent HF visits) or CV Death up to 52 Weeks after Randomisation (Confirmatory Analysis) - Full Analysis Set
		14.2.2.9.2.1 Number of Days Lost due to HF Hospitalisations (including urgent HF visits) or CV Death up to 52 Weeks after Randomisation – Per Protocol Set
		14.2.2.9.2.2 Number of Days Lost due to HF Hospitalisations (including urgent HF visits) or CV Death up to 52 Weeks after Randomisation (Confirmatory Analysis) – Per Protocol Set
		14.2.2.10.1.1 Time to CV Death up to the last available value (Sensitivity Analysis) – Full Analysis Set

Type*	Section	Title
		14.2.2.10.1.2 Time to CV Death up to the last available value (Sensitivity Analysis, Survival Estimates) – Full Analysis Set
		14.2.2.10.2,1 Time to CV Death up to the last available value (Sensitivity Analysis) – Per Protocol Set
		14.2.2.10.2.2 Time to CV Death up to the last available value (Sensitivity Analysis, Survival Estimates) – Per Protocol Set
		14.2.2.11.1.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to the last available value (Sensitivity Analysis) – Full Analysis Set
		14.2.2.11.1.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to the last available value (Sensitivity Analysis, Survival Estimates) – Full Analysis Set
		14.2.2.11.2.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to the last available value (Sensitivity Analysis) – Per Protocol Set
		14.2.2.11.2.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to the last available value (Sensitivity Analysis, Survival Estimates) – Per Protocol Set
		14.2.2.12.1.1 Time to First Event: Composite of HF Hospitalisations (including urgent HF visits) or CV Death up to the last available value (Sensitivity Analysis) – Full Analysis Set
		14.2.2.12.1.2 Time to First Event: Composite of HF Hospitalisations (including urgent HF visits) or CV Death up to the last available value (Sensitivity Analysis, Survival Estimates) – Full Analysis Set
		14.2.2.12.2.1 Time to First Event: Composite of HF Hospitalisations (including urgent HF visits) or CV Death up to the last available value (Sensitivity Analysis) – Per Protocol Set
		14.2.2.12.2.2 Time to First Event: Composite of HF Hospitalisations (including urgent HF visits) or CV Death up to the last available value (Sensitivity Analysis, Survival Estimates) – Per Protocol Set
		14.2.2.13.1.1 Composite of Recurrent HF Hospitalisations and CV Death up to 30 Days after Randomisation – Full Analysis Set
		14.2.2.13.1.2 Composite of Recurrent HF Hospitalisations and CV Death up to 30 Days after Randomisation (Confirmatory Analysis) – Full Analysis Set
		14.2.2.13.2.1 Composite of Recurrent HF Hospitalisations and CV Death up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.13.2.2 Composite of Recurrent HF Hospitalisations and CV Death up to 30 Days after Randomisation (Confirmatory Analysis) – Per Protocol Set
		14.2.2.14.1.1 Composite of Recurrent HF Hospitalisations (including urgent HF visits) and CV Death up to 30 Days after Randomisation – Full Analysis Set
		14.2.2.14.1.2 Composite of Recurrent HF Hospitalisations (including urgent HF visits) and CV Death up to 30 Days after Randomisation (Confirmatory Analysis) – Full Analysis Set

Type*	Section	Title
		14.2.2.14.2.1 Composite of Recurrent HF Hospitalisations (including urgent HF visits) and CV Death up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.14.2.2 Composite of Recurrent HF Hospitalisations (including urgent HF visits) and CV Death up to 30 Days after Randomisation (Confirmatory Analysis) – Per Protocol Set
		14.2.2.15.1.1 Composite of Recurrent CV Hospitalisations and CV Death up to 30 Days after Randomisation – Full Analysis Set
		14.2.2.15.1.2 Composite of Recurrent CV Hospitalisations and CV Death up to 30 Days after Randomisation (Confirmatory Analysis) – Full Analysis Set
		14.2.2.15.2.1 Composite of Recurrent CV Hospitalisations and CV Death up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.15.2.1 Composite of Recurrent CV Hospitalisations and CV Death up to 30 Days after Randomisation (Confirmatory Analysis) – Per Protocol Set
		14.2.2.16.1.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 30 Days after Randomisation – Full Analysis Set
		14.2.2.16.1.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 30 Days after Randomisation (Survival Estimates) – Full Analysis Set
		14.2.2.16.2.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.16.2.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 30 Days after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.17.1.1 Time to First Event: Composite of HF Hospitalisations (including urgent HF visits) or CV Death up to 30 Days after Randomisation – Full Analysis Set
		14.2.2.17.1.2 Time to First Event: Composite of HF Hospitalisations (including urgent HF visits) or CV Death up to 30 Days after Randomisation (Survival Estimates) – Full Analysis Set
		14.2.2.17.2.1 Time to First Event: Composite of HF Hospitalisations (including urgent HF visits) or CV Death up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.17.2.2 Time to First Event: Composite of HF Hospitalisations (including urgent HF visits) or CV Death up to 30 Days after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.18.1.1 Time to First Event: Composite of CV Hospitalisations or CV Death up to 30 Days after Randomisation – Full Analysis Set
		14.2.2.18.1.2 Time to First Event: Composite of CV Hospitalisations or CV Death up to 30 Days after Randomisation (Survival Estimates) – Full Analysis Set

Type*	Section	Title
		14.2.2.18.2.1 Time to First Event: Composite of CV Hospitalisations or CV Death up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.18.2.2 Time to First Event: Composite of CV Hospitalisations or CV Death up to 30 Days after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.19.1.1 Time to First Event: Composite of CV Hospitalisations or CV Death up to the last available value (Sensitivity Analysis) – Full Analysis Set
		14.2.2.19.1.2 Time to First Event: Composite of CV Hospitalisations or CV Death up to the last available value (Sensitivity Analysis, Survival Estimates) – Full Analysis Set
		14.2.2.19.2.1 Time to First Event: Composite of CV Hospitalisations or CV Death up to the last available value (Sensitivity Analysis) – Per Protocol Set
		14.2.2.19.2.2 Time to First Event: Composite of CV Hospitalisations or CV Death up to the last available value (Sensitivity Analysis, Survival Estimates) – Per Protocol Set
		14.2.2.20.1.1 Recurrent HF Hospitalisations up to 30 Days after Randomisation – Full Analysis Set
		14.2.2.20.1.2 Recurrent HF Hospitalisations up to 30 Days after Randomisation (Confirmatory Analysis) – Full Analysis Set
		14.2.2.20.2.1 Recurrent HF Hospitalisations up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.20.2.2 Recurrent HF Hospitalisations up to 30 Days after Randomisation (Confirmatory Analysis) – Per Protocol Set
		14.2.2.21.1.1 Recurrent HF Hospitalisations (including urgent HF visits) up to 30 Days after Randomisation – Full Analysis Set
		14.2.2.21.1.2 Recurrent HF Hospitalisations (including urgent HF visits) up to 30 Days after Randomisation (Confirmatory Analysis) – Full Analysis Set
		14.2.2.21.2.1 Recurrent HF Hospitalisations (including urgent HF visits) up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.21.2.2 Recurrent HF Hospitalisations (including urgent HF visits) up to 30 Days after Randomisation (Confirmatory Analysis) – Per Protocol Set
		14.2.2.22.1.1 Time to First Event: HF Hospitalisations up to 30 Days after Randomisation – Full Analysis Set
		14.2.2.22.1.2 Time to First Event: HF Hospitalisations up to 30 Days after Randomisation (Survival Estimates) – Full Analysis Set
		14.2.2.22.2.1 Time to First Event: HF Hospitalisations up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.22.2.2 Time to First Event: HF Hospitalisations up to 30 Days after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.23.1.1 Time to First Event: HF Hospitalisations up to the last available value (Sensitivity Analysis) – Full Analysis Set
		14.2.2.23.1.2 Time to First Event: HF Hospitalisations up to the last available value (Sensitivity Analysis, Survival Estimates) – Full Analysis Set

Type*	Section	Title
		14.2.2.23.2.1 Time to First Event: HF Hospitalisations up to the last available value (Sensitivity Analysis) – Per Protocol Set
		14.2.2.23.2.2 Time to First Event: HF Hospitalisations up to the last available value (Sensitivity Analysis, Survival Estimates) – Per Protocol Set
		14.2.2.24.1.1 Time to First Event: HF Hospitalisations (including urgent HF visits) up to 30 Days after Randomisation – Full Analysis Set
		14.2.2.24.1.2 Time to First Event: HF Hospitalisations (including urgent HF visits) up to 30 Days after Randomisation (Survival Estimates) – Full Analysis Set
		14.2.2.24.2.1 Time to First Event: HF Hospitalisations (including urgent HF visits) up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.24.2.2 Time to First Event: HF Hospitalisations (including urgent HF visits) up to 30 Days after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.25.1.1 Time to First Event: HF Hospitalisations (including urgent HF visits) up to the last available value (Sensitivity Analysis) – Full Analysis Set
		14.2.2.25.1.2 Time to First Event: HF Hospitalisations (including urgent HF visits) up to the last available value (Sensitivity Analysis, Survival Estimates) – Full Analysis Set
		14.2.2.25.2.1 Time to First Event: HF Hospitalisations (including urgent HF visits) up to the last available value (Sensitivity Analysis) – Per Protocol Set
		14.2.2.25.2.2 Time to First Event: HF Hospitalisations (including urgent HF visits) up to the last available value (Sensitivity Analysis, Survival Estimates) – Per Protocol Set
		14.2.2.26.1.1 Time to First Event: HF Hospitalisations up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.2.26.1.2 Time to First Event: HF Hospitalisations up to 52 Weeks after Randomisation (Survival Estimates) – Full Analysis Set
		14.2.2.26.2.1 Time to First Event: HF Hospitalisations up to 52 Weeks after Randomisation – Per Protocol Set
		14.2.2.26.2.2 Time to First Event: HF Hospitalisations up to 52 Weeks after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.27.1.1 Time to First Event: HF Hospitalisations (including urgent HF visits) up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.2.27.1.2 Time to First Event: HF Hospitalisations (including urgent HF visits) up to 52 Weeks after Randomisation (Survival Estimates) – Full Analysis Set
		14.2.2.27.2.1 Time to First Event: HF Hospitalisations (including urgent HF visits) up to 52 Weeks after Randomisation – Per Protocol Set

Type*	Section	Title
		14.2.2.27.2.2 Time to First Event: HF Hospitalisations (including urgent HF visits) up to 52 Weeks after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.28.1.1 Recurrent CV Hospitalisations up to 30 Days after Randomisation – Full Analysis Set
		14.2.2.28.1.2 Recurrent CV Hospitalisations up to 30 Days after Randomisation (Confirmatory Analysis) – Full Analysis Set
		14.2.2.28.2.1 Recurrent CV Hospitalisations up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.28.2.2 Recurrent CV Hospitalisations up to 30 Days after Randomisation (Confirmatory Analysis) – Per Protocol Set
		14.2.2.29.1.1 Recurrent CV Hospitalisations up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.2.29.1.2 Recurrent CV Hospitalisations up to 52 Weeks after Randomisation (Confirmatory Analysis) – Full Analysis Set
		14.2.2.29.2.1 Recurrent CV Hospitalisations up to 52 Weeks after Randomisation – Per Protocol Set
		14.2.2.29.2.2 Recurrent CV Hospitalisations up to 52 Weeks after Randomisation (Confirmatory Analysis) – Per Protocol Set
		14.2.2.30.1.1 Time to First Event: CV Hospitalisations up to 30 Days after Randomisation – Full Analysis Set
		14.2.2.30.1.2 Time to First Event: CV Hospitalisations up to 30 Days after Randomisation (Survival Estimates) – Full Analysis Set
		14.2.2.30.2.1 Time to First Event: CV Hospitalisations up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.30.2.2 Time to First Event: CV Hospitalisations up to 30 Days after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.31.1.1 Time to First Event: CV Hospitalisations up to the last available value (Sensitivity Analysis) – Full Analysis Set
		14.2.2.31.1.2 Time to First Event: CV Hospitalisations up to the last available value (Sensitivity Analysis, Survival Estimates) – Full Analysis Set
		14.2.2.31.2.1 Time to First Event: CV Hospitalisations up to the last available value (Sensitivity Analysis) – Per Protocol Set
		14.2.2.31.2.2 Time to First Event: CV Hospitalisations up to the last available value (Sensitivity Analysis, Survival Estimates) – Per Protocol Set
		14.2.2.32.1.1 Time to First Event: CV Hospitalisations up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.2.32.1.2 Time to First Event: CV Hospitalisations up to 52 Weeks after Randomisation (Survival Estimates) – Full Analysis Set
		14.2.2.32.2.1 Time to First Event: CV Hospitalisations up to 52 Weeks after Randomisation – Per Protocol Set
		14.2.2.32.2.2 Time to First Event: CV Hospitalisations up to 52 Weeks after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.33.1.1 Time to First Event: CV Hospitalisations or CV Death up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.2.33.1.2 Time to First Event: CV Hospitalisations or CV Death up to 52 Weeks after Randomisation (Survival Estimates) – Full Analysis Set

Type*	Section	Title
		14.2.2.33.2.1 Time to First Event: CV Hospitalisations or CV Death up to 52 Weeks after Randomisation – Per Protocol Set
		14.2.2.33.2.2 Time to First Event: CV Hospitalisations or CV Death up to 52 Weeks after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.34.1.1 Time to CV Death up to 30 Days after Randomisation – Full Analysis Set
		14.2.2.34.1.2 Time to CV Death up to 30 Days after Randomisation (Survival Estimates) – Full Analysis Set
		14.2.2.34.2.1 Time to CV Death up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.34.2.2 Time to CV Death up to 30 Days after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.35.1.1 Time to Death: All-Cause Death up to 30 Days after Randomisation – Full Analysis Set
		14.2.2.35.1.2 Time to Death: All-Cause Death up to 30 Days after Randomisation (Survival Estimates) – Full Analysis Set
		14.2.2.35.2.1 Time to Death: All-Cause Death up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.35.2.2 Time to Death: All-Cause Death up to 30 Days after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.36.1.1 Time to Death: All-Cause Death up to the last available value (Sensitivity Analysis) – Full Analysis Set
		14.2.2.36.1.2 Time to Death: All-Cause Death up to the last available value (Sensitivity Analysis, Survival Estimates) – Full Analysis Set
		14.2.2.36.2.1 Time to Death: All-Cause Death up to the last available value (Sensitivity Analysis) – Per Protocol Set
		14.2.2.36.2.2 Time to Death: All-Cause Death up to the last available value (Sensitivity Analysis, Survival Estimates) – Per Protocol Set
		14.2.2.37.1.1 Time to Death: All-Cause Death up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.2.37.1.2 Time to Death: All-Cause Death up to 52 Weeks after Randomisation (Survival Estimates) – Full Analysis Set
		14.2.2.37.2.1 Time to Death: All-Cause Death up to 52 Weeks after Randomisation – Per Protocol Set
		14.2.2.37.2.2 Time to Death: All-Cause Death up to 52 Weeks after Randomisation (Survival Estimates) – Per Protocol Set
		14.2.2.38.1 Proportion of Subjects with Events – Full Analysis Set
		14.2.2.38.2 Proportion of Subjects with Events – Per Protocol Set
		14.2.2.39.1 NYHA Functional Class - Full Analysis Set
		14.2.2.39.2 NYHA Functional Class – Per Protocol Set
		14.2.2.40.1 NYHA Functional Class (No imputation) - Full Analysis Set
		14.2.2.40.2 NYHA Functional Class (No imputation) – Per Protocol Set

Type*	Section	Title
		14.2.2.41.1 Shift Table of NYHA Classification Over Time - Full Analysis Set
		14.2.2.41.2 Shift Table of NYHA Classification Over Time – Per Protocol Set
		14.2.2.42.1.1 Number of Days Lost Due to HF Hospitalisations or CV Death up to 30 Days after Randomisation - Full Analysis Set
		14.2.2.42.1.2 Number of Days Lost Due to HF Hospitalisations or CV Death up to 30 Days after Randomisation (Confirmatory Analysis) - Full Analysis Set
		14.2.2.42.2.1 Number of Days Lost Due to HF Hospitalisations or CV Death up to 30 Days after Randomisation - Per Protocol Set
		14.2.2.42.2.2 Number of Days Lost Due to HF Hospitalisations or CV Death up to 30 Days after Randomisation (Confirmatory Analysis) - Per Protocol Set
		14.2.2.43.1.1 Number of Days Lost due to HF Hospitalisations (including urgent HF visits) or CV Death up to 30 Days after Randomisation - Full Analysis Set
		14.2.2.43.1.2 Number of Days Lost due to HF Hospitalisations (including urgent HF visits) or CV Death up to 30 Days after Randomisation (Confirmatory Analysis) - Full Analysis Set
		14.2.2.43.2.1 Number of Days Lost due to HF Hospitalisations (including urgent HF visits) or CV Death up to 30 Days after Randomisation – Per Protocol Set
		14.2.2.43.2.2 Number of Days Lost due to HF Hospitalisations (including urgent HF visits) or CV Death up to 30 Days after Randomisation (Confirmatory Analysis) – Per Protocol Set
	14.2.3 Subgroup Analyses	14.2.3.1.1.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Hb level at baseline - Full Analysis Set
		14.2.3.1.1.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Hb level at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.1.2.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline - Full Analysis Set
		14.2.3.1.2.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.1.3.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline by tertiles - Full Analysis Set
		14.2.3.1.3.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline by tertiles (Confirmatory Analysis) - Full Analysis Set

Type*	Section	Title
		14.2.3.1.4.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline - Full Analysis Set
		14.2.3.1.4.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.1.5.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline by tertiles- Full Analysis Set
		14.2.3.1.5.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline by tertiles (Confirmatory Analysis) - Full Analysis Set
		14.2.3.1.6.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Sex - Full Analysis Set
		14.2.3.1.6.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Sex (Confirmatory Analysis) - Full Analysis Set
		14.2.3.1.7.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Age - Full Analysis Set
		14.2.3.1.7.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Age (Confirmatory Analysis) - Full Analysis Set
		14.2.3.1.8.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Renal function at baseline - Full Analysis Set
		14.2.3.1.8.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Renal function at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.1.9.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Ischaemic Aetiology of HF - Full Analysis Set
		14.2.3.1.9.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Ischaemic Aetiology of HF (Confirmatory Analysis) - Full Analysis Set
		14.2.3.1.10.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of NYHA at baseline - Full Analysis Set
		14.2.3.1.10.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of NYHA at baseline (Confirmatory Analysis) - Full Analysis Set

Type*	Section	Title
		14.2.3.1.11.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of NT-pro BNP and BNP at baseline - Full Analysis Set
		14.2.3.1.11.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of NT-pro BNP and BNP at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.1.12.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Left ventricular ejection fraction (%) at baseline - Full Analysis Set
		14.2.3.1.12.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Left ventricular ejection fraction (%) at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.1.13.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Diagnosis of Heart Failure - Full Analysis Set
		14.2.3.1.13.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Diagnosis of Heart Failure (Confirmatory Analysis) - Full Analysis Set
		14.2.3.1.14.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Hospitalisation for Acute Heart Failure in the 12 months prior Index Hospitalisation - Full Analysis Set
		14.2.3.1.14.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Hospitalisation for Acute Heart Failure in the 12 months prior Index Hospitalisation (Confirmatory Analysis) - Full Analysis Set
		14.2.3.1.15.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Creatinine at baseline - Full Analysis Set
		14.2.3.1.15.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Creatinine at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.1.16.1 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of eGFR at baseline - Full Analysis Set
		14.2.3.1.16.2 Recurrent HF Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of eGFR at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.1.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Hb level at baseline - Full Analysis Set

Type*	Section	Title
		14.2.3.2.1.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Hb level at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.2.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline - Full Analysis Set
		14.2.3.2.2.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.3.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline by tertiles- Full Analysis Set
		14.2.3.2.3.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline by tertiles (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.4.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline - Full Analysis Set
		14.2.3.2.4.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.5.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline by tertiles- Full Analysis Set
		14.2.3.2.5.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline by tertiles (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.6.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Sex - Full Analysis Set
		14.2.3.2.6.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Sex (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.7.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Age - Full Analysis Set
		14.2.3.2.7.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Age (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.8.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Renal function at baseline - Full Analysis Set

Type*	Section	Title
		14.2.3.2.8.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Renal function at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.9.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Ischaemic Aetiology of HF - Full Analysis Set
		14.2.3.2.9.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Ischaemic Aetiology of HF (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.10.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of NYHA at baseline - Full Analysis Set
		14.2.3.2.10.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of NYHA at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.11.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of NT-pro BNP and BNP at baseline - Full Analysis Set
		14.2.3.2.11.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of NT-pro BNP and BNP at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.12.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Left ventricular ejection fraction (%) at baseline - Full Analysis Set
		14.2.3.2.12.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Left ventricular ejection fraction (%) at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.13.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Diagnosis of Heart Failure - Full Analysis Set
		14.2.3.2.13.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Diagnosis of Heart Failure (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.14.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Hospitalisation for Acute Heart Failure in the 12 months prior Index Hospitalisation - Full Analysis Set
		14.2.3.2.14.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Hospitalisation for Acute Heart Failure in the 12 months prior Index Hospitalisation (Confirmatory Analysis) - Full Analysis Set

Type*	Section	Title
		14.2.3.2.15.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Creatinine at baseline - Full Analysis Set
		14.2.3.2.15.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of Creatinine at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.2.16.1 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of eGFR at baseline - Full Analysis Set
		14.2.3.2.16.2 Recurrent CV Hospitalisations and CV Death up to 52 Weeks after Randomisation – Subgroup of eGFR at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.3.1.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Hb level at baseline - Full Analysis Set
		14.2.3.3.1.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Hb level at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.3.2.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline - Full Analysis Set
		14.2.3.3.2.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline - Full Analysis Set
		14.2.3.3.3.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline by tertiles - Full Analysis Set
		14.2.3.3.3.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline by tertiles - Full Analysis Set
		14.2.3.3.4.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline - Full Analysis Set
		14.2.3.3.4.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.3.5.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline by tertiles - Full Analysis Set

Type*	Section	Title
		14.2.3.3.5.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline by tertiles (Confirmatory Analysis) - Full Analysis Set
		14.2.3.3.6.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Sex - Full Analysis Set
		14.2.3.3.6.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Sex (Confirmatory Analysis) - Full Analysis Set
		14.2.3.3.7.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Age - Full Analysis Set
		14.2.3.3.7.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Age (Confirmatory Analysis) - Full Analysis Set
		14.2.3.3.8.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Renal function at baseline - Full Analysis Set
		14.2.3.3.8.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Renal function at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.3.9.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Ischaemic Aetiology of HF - Full Analysis Set
		14.2.3.3.9.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Ischaemic Aetiology of HF (Confirmatory Analysis) - Full Analysis Set
		14.2.3.3.10.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of NYHA at baseline - Full Analysis Set
		14.2.3.3.10.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of NYHA at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.3.11.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of NT-pro BNP and BNP at baseline - Full Analysis Set
		14.2.3.3.11.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of NT-pro BNP and BNP at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.3.12.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Left ventricular ejection fraction (%) at baseline - Full Analysis Set

Type*	Section	Title
		14.2.3.3.12.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Left ventricular ejection fraction (%) at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.3.13.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Diagnosis of Heart Failure - Full Analysis Set
		14.2.3.3.13.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Diagnosis of Heart Failure (Confirmatory Analysis) - Full Analysis Set
		14.2.3.3.14.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Hospitalisation for Acute Heart Failure in the 12 months prior Index Hospitalisation - Full Analysis Set
		14.2.3.3.14.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Hospitalisation for Acute Heart Failure in the 12 months prior Index Hospitalisation (Confirmatory Analysis) - Full Analysis Set
		14.2.3.3.15.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Creatinine at baseline - Full Analysis Set
		14.2.3.3.15.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of Creatinine at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.3.16.1 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of eGFR at baseline - Full Analysis Set
		14.2.3.3.16.2 Recurrent HF Hospitalisations up to 52 Weeks after Randomisation – Subgroup of eGFR at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.4.1.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Hb level at baseline - Full Analysis Set
		14.2.3.4.1.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Hb level at baseline (Survival Estimates) - Full Analysis Set
		14.2.3.4.2.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline - Full Analysis Set
		14.2.3.4.2.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline (Survival Estimates) - Full Analysis Set
		14.2.3.4.3.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline by tertiles - Full Analysis Set

Type*	Section	Title
		14.2.3.4.3.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline by tertiles (Survival Estimates) - Full Analysis Set
		14.2.3.4.4.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline - Full Analysis Set
		14.2.3.4.4.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline (Survival Estimates) - Full Analysis Set
		14.2.3.4.5.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline by tertiles - Full Analysis Set
		14.2.3.4.5.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline by tertiles (Survival Estimates) - Full Analysis Set
		14.2.3.4.6.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Sex - Full Analysis Set
		14.2.3.4.6.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Sex (Survival Estimates) - Full Analysis Set
		14.2.3.4.7.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Age - Full Analysis Set
		14.2.3.4.7.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Age (Survival Estimates) - Full Analysis Set
		14.2.3.4.8.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Renal function at baseline - Full Analysis Set
		14.2.3.4.8.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Renal function at baseline (Survival Estimates) - Full Analysis Set
		14.2.3.4.9.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Ischaemic Aetiology of HF - Full Analysis Set
		14.2.3.4.9.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Ischaemic Aetiology of HF (Survival Estimates) - Full Analysis Set
		14.2.3.4.10.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of NYHA at baseline - Full Analysis Set
		14.2.3.4.10.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of NYHA at baseline (Survival Estimates) - Full Analysis Set
		14.2.3.4.11.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of NT-pro BNP and BNP at baseline - Full Analysis Set
		14.2.3.4.11.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of NT-pro BNP and BNP at baseline (Survival Estimates) - Full Analysis Set

Type*	Section	Title
		14.2.3.4.12.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Left ventricular ejection fraction (%) at baseline - Full Analysis Set
		14.2.3.4.12.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Left ventricular ejection fraction (%) at baseline (Survival Estimates) - Full Analysis Set
		14.2.3.4.13.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Diagnosis of Heart Failure - Full Analysis Set
		14.2.3.4.13.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Diagnosis of Heart Failure (Survival Estimates) - Full Analysis Set
		14.2.3.4.14.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Hospitalisation for Acute Heart Failure in the 12 months prior Index Hospitalisation - Full Analysis Set
		14.2.3.4.14.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Hospitalisation for Acute Heart Failure in the 12 months prior Index Hospitalisation (Survival Estimates) - Full Analysis Set
		14.2.3.4.15.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Creatinine at baseline - Full Analysis Set
		14.2.3.4.15.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of Creatinine at baseline (Survival Estimates) - Full Analysis Set
		14.2.3.4.16.1 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of eGFR at baseline - Full Analysis Set
		14.2.3.4.16.2 Time to CV Death up to 52 Weeks after Randomisation – Subgroup of eGFR at baseline (Survival Estimates) - Full Analysis Set
		14.2.3.5.1.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Hb level at baseline - Full Analysis Set
		14.2.3.5.1.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Hb level at baseline (Survival Estimates) - Full Analysis Set
		14.2.3.5.2.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline - Full Analysis Set
		14.2.3.5.2.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline (Survival Estimates) - Full Analysis Set

Type*	Section	Title
		14.2.3.5.3.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline by tertiles - Full Analysis Set
		14.2.3.5.3.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline by tertiles (Survival Estimates) - Full Analysis Set
		14.2.3.5.4.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline - Full Analysis Set
		14.2.3.5.4.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline (Survival Estimates) - Full Analysis Set
		14.2.3.5.5.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline by tertiles - Full Analysis Set
		14.2.3.5.5.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline by tertiles (Survival Estimates) - Full Analysis Set
		14.2.3.5.6.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Sex - Full Analysis Set
		14.2.3.5.6.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Sex (Survival Estimates) - Full Analysis Set
		14.2.3.5.7.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Age - Full Analysis Set
		14.2.3.5.7.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Age (Survival Estimates) - Full Analysis Set
		14.2.3.5.8.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Renal function at baseline - Full Analysis Set
		14.2.3.5.8.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Renal function at baseline (Survival Estimates) - Full Analysis Set
		14.2.3.5.9.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Ischaemic Aetiology of HF - Full Analysis Set

Type*	Section	Title
		14.2.3.5.9.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Ischaemic Aetiology of HF (Survival Estimates) - Full Analysis Set
		14.2.3.5.10.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of NYHA at baseline - Full Analysis Set
		14.2.3.5.10.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of NYHA at baseline (Survival Estimates) - Full Analysis Set
		14.2.3.5.11.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of NT-pro BNP and BNP at baseline - Full Analysis Set
		14.2.3.5.11.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of NT-pro BNP and BNP at baseline (Survival Estimates) - Full Analysis Set
		14.2.3.5.12.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Left ventricular ejection fraction (%) at baseline - Full Analysis Set
		14.2.3.5.12.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Left ventricular ejection fraction (%) at baseline (Survival Estimates) - Full Analysis Set
		14.2.3.5.13.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Diagnosis of Heart Failure - Full Analysis Set
		14.2.3.5.13.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Diagnosis of Heart Failure (Survival Estimates) - Full Analysis Set
		14.2.3.5.14.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Hospitalisation for Acute Heart Failure in the 12 months prior Index Hospitalisation - Full Analysis Set
		14.2.3.5.14.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Hospitalisation for Acute Heart Failure in the 12 months prior Index Hospitalisation (Survival Estimates) - Full Analysis Set
		14.2.3.5.15.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Creatinine at baseline - Full Analysis Set
		14.2.3.5.15.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Creatinine at Baseline (Survival Estimates) - Full Analysis Set

Type*	Section	Title
		14.2.3.5.16.1 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of eGFR at baseline - Full Analysis Set
		14.2.3.5.16.2 Time to First Event: Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of eGFR at Baseline (Survival Estimates) - Full Analysis Set
		14.2.3.6.1.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Hb level at baseline - Full Analysis Set
		14.2.3.6.1.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Hb level at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.6.2.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline - Full Analysis Set
		14.2.3.6.2.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.6.3.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline by tertiles - Full Analysis Set
		14.2.3.6.3.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Ferritin level at baseline by tertiles (Confirmatory Analysis) - Full Analysis Set
		14.2.3.6.4.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline - Full Analysis Set
		14.2.3.6.4.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.6.5.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline by tertiles - Full Analysis Set
		14.2.3.6.5.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of TSAT category at baseline by tertiles (Confirmatory Analysis) - Full Analysis Set
		14.2.3.6.6.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Sex - Full Analysis Set

Type*	Section	Title
		14.2.3.6.6.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Sex (Confirmatory Analysis) - Full Analysis Set
		14.2.3.6.7.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Age - Full Analysis Set
		14.2.3.6.7.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Age (Confirmatory Analysis) - Full Analysis Set
		14.2.3.6.8.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Renal function at baseline - Full Analysis Set
		14.2.3.6.8.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Renal function at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.6.9.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Ischaemic Aetiology of HF - Full Analysis Set
		14.2.3.6.9.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Ischaemic Aetiology of HF (Confirmatory Analysis) - Full Analysis Set
		14.2.3.6.10.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of NYHA at baseline - Full Analysis Set
		14.2.3.6.10.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of NYHA at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.6.11.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of NT-pro BNP and BNP at baseline - Full Analysis Set
		14.2.3.6.11.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of NT-pro BNP and BNP at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.6.12.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Left ventricular ejection fraction (%) at baseline - Full Analysis Set
		14.2.3.6.12.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Left ventricular ejection fraction (%) at baseline (Confirmatory Analysis) - Full Analysis Set

Type*	Section	Title
		14.2.3.6.13.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Diagnosis of Heart Failure - Full Analysis Set
		14.2.3.6.13.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Diagnosis of Heart Failure (Confirmatory Analysis) - Full Analysis Set
		14.2.3.6.14.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Hospitalisation for Acute Heart Failure in the 12 months prior Index Hospitalisation - Full Analysis Set
		14.2.3.6.14.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Hospitalisation for Acute Heart Failure in the 12 months prior Index Hospitalisation (Confirmatory Analysis) - Full Analysis Set
		14.2.3.6.15.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Creatinine at baseline - Full Analysis Set
		14.2.3.6.15.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of Creatinine at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.6.16.1 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of eGFR at baseline - Full Analysis Set
		14.2.3.6.16.2 Number of Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Subgroup of eGFR at baseline (Confirmatory Analysis) - Full Analysis Set
		14.2.3.7.1 NYHA Functional Class – Subgroup of Hb level at baseline - Full Analysis Set
		14.2.3.7.2 NYHA Functional Class – Subgroup of Ferritin level at baseline - Full Analysis Set
		14.2.3.7.3 NYHA Functional Class – Subgroup of Ferritin level at baseline by tertiles - Full Analysis Set
		14.2.3.7.4 NYHA Functional Class – Subgroup of TSAT category at baseline - Full Analysis Set
		14.2.3.7.5 NYHA Functional Class – Subgroup of TSAT category at baseline by tertiles - Full Analysis Set
		14.2.3.7.6 NYHA Functional Class – Subgroup of Sex - Full Analysis Set
		14.2.3.7.7 NYHA Functional Class – Subgroup of Age - Full Analysis Set
		14.2.3.7.8 NYHA Functional Class – Subgroup of Renal function at baseline - Full Analysis Set
		14.2.3.7.9 NYHA Functional Class – Subgroup of Ischaemic Aetiology of HF - Full Analysis Set

Type*	Section	Title
		14.2.3.7.10 NYHA Functional Class – Subgroup of NYHA at baseline - Full Analysis Set
		14.2.3.7.11 NYHA Functional Class – Subgroup of NT-pro BNP and BNP at baseline - Full Analysis Set
		14.2.3.7.12 NYHA Functional Class – Subgroup of Left ventricular ejection fraction (%) at baseline - Full Analysis Set
		14.2.3.7.13 NYHA Functional Class – Subgroup of Diagnosis of Heart Failure - Full Analysis Set
		14.2.3.7.14 NYHA Functional Class – Subgroup of Hospitalisation for Acute Heart Failure in the 12 months prior Index Hospitalisation - Full Analysis Set
		14.2.3.7.15 NYHA Functional Class – Subgroup of Creatinine at baseline - Full Analysis Set
		14.2.3.7.16 NYHA Functional Class – Subgroup of eGFR at baseline - Full Analysis Set
T	14.3 Safety	14.3.1.1 Overview of Adverse Events – Safety Analysis Set
		14.3.1.2 TEAEs by System Organ Class, Preferred Term and Treatment Group – Safety Analysis Set
		14.3.1.3 TEAEs Related to Study Product by System Organ Class, Preferred Term and Treatment Group – Safety Analysis Set
		14.3.1.4 TEAEs by System Organ Class, Preferred Term, Relationship to Study Product and Treatment Group – Safety Analysis Set
		14.3.1.5 Severe TEAEs by System Organ Class, Preferred Term and Treatment Group – Safety Analysis Set
		14.3.1.6 TEAEs by System Organ Class, Preferred Term, Severity and Treatment Group – Safety Analysis Set
		14.3.1.7 Serious TEAEs by System Organ Class, Preferred Term and Treatment Group – Safety Analysis Set
		14.3.1.8 Serious TEAEs occurring in >5% of subjects by System Organ Class, Preferred Term and Treatment Group – Safety Analysis Set
		14.3.1.9 Non-serious TEAEs by System Organ Class, Preferred Term and Treatment Group – Safety Analysis Set
		14.3.1.10 Serious TEAEs Related to Study Product by System Organ Class, Preferred Term and Treatment Group – Safety Analysis Set
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		14.3.1.12 TEAEs Leading to Study Discontinuation by System Organ Class, Preferred Term and Treatment Group – Safety Analysis Set
		14.3.1.13 Serious TEAEs by System Organ Class, Preferred Term, Severity and Treatment Group – Safety Analysis Set
		14.3.1.14 Fatal TEAEs by System Organ Class, Preferred Term and Treatment Group – Safety Analysis Set
		14.3.1.15 Fatal TEAEs Related to Study Product by System Organ Class, Preferred Term and Treatment Group – Safety Analysis Set

Type*	Section	Title
		14.3.1.16 TEAEs of Clinical Interest by Event Type, Preferred Term and Treatment Group – Safety Analysis Set
		14.3.1.17 TEAEs of Special Interest Related to Study Product by Event Type, Preferred Term and Treatment Group – Safety Analysis Set
L	14.3.2 AE Listings	14.3.2.1 TEAEs Related to Study Product – Safety Analysis Set
		14.3.2.2 Serious TEAEs Related to Study Product – Safety Analysis Set
		14.3.2.3 Fatal Adverse Events – Safety Analysis Set
L	14.3.4 Labs Listing	14.3.4 Abnormal Laboratory Values – Safety Analysis Set
T	14.4 Other Safety	14.4.1.1 Summary of Event Adjudications Performed by CEC – Safety Analysis Set
		14.4.2.1 Summary of Special Situation Events – Safety Analysis Set
		14.4.3.1.1 Laboratory Values: Actual Values and Changes from Baseline by Analysis Visit for Serum ferritin (ng/mL) – Safety Analysis Set
		14.4.3.1.2 Laboratory Values: Actual Values and Changes from Baseline by Analysis Visit for Haemoglobin (g/L) – Safety Analysis Set
		14.4.3.1.3 Laboratory Values: Actual Values and Changes from Baseline by Analysis Visit for Transferrin saturation (%) – Safety Analysis Set
		14.4.3.1.4 Laboratory Values: Actual Values and Changes from Baseline by Analysis Visit for Phosphorus (mg/dL) – Safety Analysis Set
		14.4.3.2.1 Shift from Baseline and Post-Baseline Analysis visits for Normal versus Abnormal Laboratory Values for Serum ferritin (ng/mL) – Safety Analysis Set
		14.4.3.2.2 Shift from Baseline and Post-Baseline Analysis visits for Normal versus Abnormal Laboratory Values for Haemoglobin (g/L)– Safety Analysis Set
		14.4.3.2.3 Shift from Baseline and Post-Baseline Analysis visits for Normal versus Abnormal Laboratory Values for Transferrin saturation (%) – Safety Analysis Set
		14.4.3.2.4 Shift from Baseline and Post-Baseline Analysis visits for Normal versus Abnormal Laboratory Values for Phosphorus (mg/dL) – Safety Analysis Set
		14.4.3.3 Shift from Baseline and Post-Baseline Analysis visits and Lowest Post-Baseline Value for Phosphorus (mg/dL) – Safety Analysis Set
		14.4.4.1.1 Vital Signs: Actual Values and Changes from Baseline by Analysis Visit for Height (cm)– Safety Analysis Set
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Type*	Section	Title
		14.4.4.1.3 Vital Signs: Actual Values and Changes from Baseline by Analysis Visit for Systolic blood pressure (mmHg) – Safety Analysis Set
		14.4.4.1.4 Vital Signs: Actual Values and Changes from Baseline by Analysis Visit for Diastolic blood pressure (mmHg)– Safety Analysis Set
		14.4.4.1.5 Vital Signs: Actual Values and Changes from Baseline by Analysis Visit for Heart rate (beats/min) – Safety Analysis Set
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		14.5.1.2.1 KCCQ-12 Repeated-Measures Model for Analysis of Treatment Difference (Overall Summary Score) – Full Analysis Set
		14.5.1.2.2 KCCQ-12 Repeated-Measures Model for Analysis of Treatment Difference (Overall Summary Score) – Per Protocol Set
		14.5.1.3.1 KCCQ-12 Repeated-Measures Model for Analysis of Treatment Difference (Clinical Summary Score) – Full Analysis Set
		14.5.1.3.2 KCCQ-12 Repeated-Measures Model for Analysis of Treatment Difference (Clinical Summary Score) – Per Protocol Set
		14.5.1.4.1 EQ-5D-5L: Individual Categories – Full Analysis Set
		14.5.1.4.2 EQ-5D-5L: Individual Categories – Per Protocol Set
		14.5.1.5.1 EQ-5D-5L VAS and Index Score: Actual Values and Changes from Baseline – Full Analysis Set
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		14.5.1.6.1 EQ-5D-5L Repeated-Measures Model for Analysis of Treatment Difference (Index Score)– Full Analysis Set
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Type*	Section	Title
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		16.2.1.2 Randomisation Scheme and Codes (Subject Identification) – All Randomised Set
		16.2.1.3 Start of Treatment after Randomisation Date – All Randomised Set
		16.2.2.1.1 Description of Inclusion and Exclusion Criteria
		16.2.2.1.2 Inclusion and Exclusion Criteria – Screen Failure Subjects
		16.2.2.2 Admission and Discharge Dates – All Randomised Set
		16.2.2.3.1 Description of Protocol Violation Categories
		16.2.2.3.2 Protocol Violations – All Randomised Set
		16.2.3.1 Subject Populations – All Screened Set
		16.2.3.2 Subjects Excluded from Efficacy Analyses – All Randomised Set
		16.2.4.1.1 Demographics – All Randomised Set
		16.2.4.1.2 Demographics – Screen Failure Subjects
		16.2.4.2 Index Hospitalisation Information – All Randomised Set
		16.2.4.3 History of Cardiovascular Risk Factors – All Randomised Set
		16.2.4.4 Symptoms and Signs of Heart Failure at Time of Index Hospitalisation – All Randomised Set
		16.2.4.5 Other Baseline Disease Characteristics – All Randomised Set
		16.2.4.6 Acute Heart Failure Hospitalisation History – All Randomised Set
		16.2.4.7 Medical History – All Randomised Set
		16.2.4.8 Acute Heart Failure Local Laboratory Blood Test – All Randomised Set
		16.2.5.1 Dosing Information – Safety Analysis Set
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		16.2.6.1 Efficacy Response Data up to 52 Weeks after Randomisation – Full Analysis Set
		16.2.6.2 Efficacy Response Data up to 30 Days after Randomisation – Full Analysis Set
		16.2.6.3 Efficacy Response Data up to the Last available value – Full Analysis Set
		16.2.6.4.1 Events Adjudicated by Clinical Endpoint Committee – Full Analysis Set
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		16.2.6.5 Hospitalisation Details – Full Analysis Set
		16.2.6.6 NYHA Functional Class – Full Analysis Set
		16.2.7.1 All Adverse Events – Safety Analysis Set
		16.2.7.2 Serious Adverse Events – Safety Analysis Set
		16.2.7.3 Adverse Events Leading to Study Product Discontinuation – Safety Analysis Set
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		16.2.7.5 Hypersensitivity Reactions – Safety Analysis Set
		16.2.7.6 Non-Treatment Emergent Adverse Events – Safety Analysis Set
		16.2.7.7 Adverse Events between Randomisation and Start of Treatment – Safety Analysis Set
		16.2.8.1 Local Laboratory Results – Safety Analysis Set

Type*	Section	Title
		16.2.8.2 Serum Pregnancy Test – Safety Analysis Set
		16.2.9.1 Vital Signs – Safety Analysis Set
		16.2.9.2 Electrocardiograms – Safety Analysis Set
		16.2.9.3 Special Situations – Full Analysis Set
		16.2.9.4 Symptoms and Signs of Heart Failure – Full Analysis Set
		16.2.9.5 Concomitant and Prior Medications – Full Analysis Set
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		16.2.9.7 Pregnancy – Details of Mother and Current Pregnancy – Full Analysis Set
		16.2.9.8 Pregnancy – Drug Exposure during Pregnancy – Full Analysis Set
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		16.2.10.1 KCCQ-12 – Full Analysis Set
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F	14.1 Disposition/Demographics/Other Characteristics	14.1.1.1 KM Curves for Time to Discontinuation – Full Analysis Set
F	14.2 Efficacy	14.2.1.1 Cumulative Risk over Time for HF Hospitalisations or CV Deaths– Full Analysis Set
		14.2.1.2 Cumulative Risk over Time for HF Hospitalisations or CV Deaths– Per Protocol Set
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		14.2.2.1.2 Cumulative Risk over Time for CV Hospitalisations or CV Deaths– Per Protocol Set
		14.2.2.2.1 Cumulative Risk over Time for HF Hospitalisations – Full Analysis Set
		14.2.2.2.2 Cumulative Risk over Time for HF Hospitalisations – Per Protocol Set
		14.2.2.3.1 Cumulative Risk over Time for CV Hospitalisations – Full Analysis Set
		14.2.2.3.2 Cumulative Risk over Time for CV Hospitalisations – Per Protocol Set
F	14.2.3 Subgroup Analyses	14.2.3.1 Forest Plot of Rate Ratios for HF Hospitalisations and CV Deaths up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.3.2 Forest Plot of Rate Ratios for CV Hospitalisations and CV Deaths up to 52 Weeks after Randomisation – Full Analysis Set
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		14.2.3.5 Forest Plot of Hazard Ratios for Composite of HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Full Analysis Set
		14.2.3.6 Forest Plot of Rate Ratios for Days Lost due to HF Hospitalisations or CV Death up to 52 Weeks after Randomisation – Full Analysis Set

Type*	Section	Title
		14.2.3.7 Forest Plot of Odds Ratios for NYHA Functional Class – Full Analysis Set

*T = Table, L = Listing, F = Figure.

8. APPENDICES

Appendix I: Protocol Deviations

	Standard name of the deviation	Deviation code	Major/Potentially Critical	Statistical Assessment of the deviations
	Inclusion Criteria			
1	Hospitalised for ADHF, one of the following items a to d not confirmed: a) Upon admission for the AHF episode, persistent dyspnoea at rest in a recumbent sitting position (30-45o) or with minimal exertion b) Upon or during the AHF admission, at least two 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 iv. Elevated jugular venous pressure (> 8cm H2O) c. Natriuretic peptide levels, measured ≤72 hours (for protocol version 3.0) or ≤24 hours (for protocol version 1.1, 2.0) 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 (for protocol version 2.0, 3.0) d. AHF episode treated with minimally 40 mg of IV furosemide (or equivalent IV loop diuretic defined as 20 mg of torsemide or 1 mg of bumetanide)	PDINC01	Major	Excluded from PP
2	Subject is not or not confirmed iron deficient defined as serum ferritin <100 ng/mL or 100 ng/mL ≤ serum ferritin ≤299 ng/mL if TSAT <20%.	PDINC02	Major	Excluded from PP

	Standard name of the deviation	Deviation code	Major/Potentially Critical	Statistical Assessment of the deviations
3	Subject not having a Left ventricular ejection fraction <50% (assessed and documented within 12 months prior to randomisation).	PDINC03	Major	Excluded from PP
4	Subject not male or female aged ≥18 years old	PDINC04	Major	Excluded from PP
5	Subject (or legally acceptable representative) has not provided the appropriate written informed consent. Subject must provide written informed consent before any study-specific procedures are performed	PDINC05	Major	Excluded from the analyses (FAS and PP)
	Exclusion Criteria			
1	Subject with 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).	PDEXC01	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
2	Subject with 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.	PDEXC02	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
3	Subject with documented restricted amyloid myocardiopathy, or acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy.	PDEXC03	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
4	Subject with clinical evidence of acute coronary syndrome, transient ischemic attack or stroke, within the last 30 days prior randomisation	PDEXC04	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
5	Subject with severe valvular or left ventricular outflow obstruction disease needing intervention.	PDEXC05	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
6	Subject with coronary-artery bypass graft, cardiac resynchronisation therapy device implantation, percutaneous intervention (e.g., cardiac, cerebrovascular, aortic) or major surgery that led to significant blood loss, including thoracic and cardiac surgery, within the last 3 months prior to randomisation.	PDEXC06	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)

	Standard name of the deviation	Deviation code	Major/Potentially Critical	Statistical Assessment of the deviations
7	Subject has a body weight <35 kg at randomisation	PDEXC07	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
8	Subject randomized despite an immediate need of transfusion or with a Hb <8 g/dL or with a Hb >15 g/dL	PDEXC08	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
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.	PDEXC09	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
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.	PDEXC10	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
11	Subject with a known hypersensitivity to any of the study products to be administered or known serious hypersensitivity to other parenteral iron products	PDEXC11	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
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).	PDEXC12	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
13	Subject with a history of erythropoietin stimulating agent, IV iron therapy, and/or blood transfusion in previous 3 months prior to randomisation.	PDEXC13	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
14	Subject on treatment with oral iron therapy at doses >100 mg/day in previous 4 weeks prior to randomisation.	PDEXC14	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
15	Subjects currently receiving systemic chemotherapy and/or radiotherapy.	PDEXC15	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)

	Standard name of the deviation	Deviation code	Major/Potentially Critical	Statistical Assessment of the deviations
16	Subjects on renal dialysis (previous, current or planned within the next 6 months).	PDEXC16	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
17	Subject has known history of malignancy of any organ system (except non-invasive basal cell carcinoma, squamous cell carcinoma of the skin or cervical intra-epithelial neoplasia) within the last 5 years	PDEXC17	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
18	Subject has a terminal illness other than HF with expected survival <12 months.	PDEXC18	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
19	Subjects with a chronic liver disease (including active hepatitis) and/or alanine transaminase or aspartate transaminase above 3 times the upper limit of the normal range.	PDEXC19	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
20	Subjects with known hepatitis B surface antigen positivity and/or hepatitis C virus ribonucleic acid positivity.	PDEXC20	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
21	Subject previously randomised into this study.	PDEXC21	Major	Major: Other action - Subject will only be handled in the ITT population with the first enrolment into the study
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).	PDEXC22	Major/minor case by case review required	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
23	Subject is pregnant (e.g., positive human chorionic gonadotropin test) or breast feeding.	PDEXC23	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
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.	PDEXC24	Major/minor case by case review required	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)

	Standard name of the deviation	Deviation code	Major/Potentially Critical	Statistical Assessment of the deviations
25	Subject has a history of drug or alcohol abuse within 2 years prior to screening.	PDEXC25	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
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.	PDEXC26	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
	Study procedures			
1	In case of ICF updates during the course of the study: Subject (or legally acceptable representative) has not provided the appropriate written informed reconsent in case of an informed consent update.	*PDSPR01*	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
2	Subject (or legally acceptable representative) has not provided the appropriate written informed consent for the Biomarker sub-study but samples were collected.	*PDSPR01b*	Major	None
3	Subjects with missing local laboratory assessment specific to the study (or with local lab values not evaluable due to logistical reasons, eg wrong handling of samples) or missing physical examination.	*PDSPR02*	Minor	None
4	Subjects with local Lab results missing at post randomization visits to determine if ID persists and to obtain Hb values	*PDSPR03*	Major	None
5	Subjects with not completed KCCQ, EQ-5D questionnaires and/or not available NYHA classification.	*PDSPR04*	Minor	None
6	Subjects with missing ECG assessment at baseline and Visit 6 or with a missing ECG scan uploaded in the eCRF.	*PDSPR05*	Minor	None
7	Subjects with study visit OOW as defined in the protocol	*PDSPR06*	Minor	None
8	Subjects with missed study visit (phone or on-site)	*PDSPR07*	Major	None

	Standard name of the deviation	Deviation code	Major/Potentially Critical	Statistical Assessment of the deviations
9	Subjects that consented for the biomarker substudy but with biomarker sample collection missing (or with local lab values not evaluable due to logistical reasons, eg wrong handling of samples); Or other deviations to biomarker sampling	*PDSPR08*	Minor	None
10	Subject anonymity is not maintained in source documents uploaded ECGs, for SAE/safety and / or adjudication purposes.	*PDSPR09*	Major	None
11	Subjects with study visits performed as telephone calls instead of physical visits	*PDSPR10*	Minor	None
12	Subjects with assessments done in extent to the protocol defined assessments at respective visits (eg additional EQ5D questionnaires at additional visits)	*PDSPR11*	Minor	None
13	Subjects with assessments done at visits in the wrong order (eg lab assessments prior the questionnaires, questionnaires at the day of the visits/calls or collecting the laboratory values from different blood drawings) or by the wrong study staff	*PDSPR12*	Minor	None
14	Subjects received treatment prior stabilisation from IV diuretics	*PDSPR13*	Minor	None
15	Site blinding plan not followed (study staff performing assessments not assigned to)	*PDSPR14*	Major	None
16	Post-randomisation study drug given based on Labs done more than 7 days	*PDSPR15*	Minor	None
17	Inconsistencies in the ICF consent procedure e.g. date differences…	*PDSPR16*	Major	None
	Investigational Medicinal Product			
1	Subjects who received Incorrect IMP dosing based on subject BW at baseline & Hb value at screening	PDIMP01	Major	Excluded from PP
2	Subjects with ID who was administered Incorrect IMP dosing based on subject BW & Hb value at post-baseline dosing visits (Weeks 6, 12, 24) or subject without ID who was administered IMP dosing post-baseline - lower dosage than assigned	PDIMP02a	Major	Excluded from PP

	Standard name of the deviation	Deviation code	Major/Potentially Critical	Statistical Assessment of the deviations
	Subjects with ID who was administered Incorrect IMP dosing based on subject BW & Hb value at post-baseline dosing visits (Weeks 6, 12, 24) or subject without ID who was administered IMP dosing post-baseline -- higher dosage than assigned	PDIMP02b	Major	Excluded from PP
3	Subject who missed one or more doses of IMP	PDIMP03	Major	Excluded from PP
4	Subject received incorrect treatment allocation	PDIMP04	Major	None
5	Subject received treatment but failed to attend any post-baseline visit or assessment	PDIMP05	Major	Excluded from the analyses (FAS and PP)
6	Subject received study treatment not according to the administration guidelines (including undiluted bolus IV injection, duration of injection, using blinding measures as a black syringe or a curtain)	PDIMP06	Major	None
7	Subjects with IMP administered by someone other than assigned unblinded study staff	PDIMP07	Major	None
8	Subjects with events that led to unblinding of the study treatment without an emergency situation	PDIMP08	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
9	Subjects with dosing of IMP not at the time point of randomization prior discharge, or randomization not done at last day of hospital discharge	PDIMP09	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
10	Deviations on IMP handling like, shipment destruction prior IMP reconciliation is made or IMP storage	PDIMP10	Minor	None
11	Subjects with administration of expired IMP or IMP with deviations in the temperature log	PDIMP11	Major	Excluded from PP
12	Subject took study treatment after intake of forbidden Concomitant medication	PDIMP12	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
	Other			

	Standard name of the deviation	Deviation code	Major/Potentially Critical	Statistical Assessment of the deviations
1	Unreported SAE detected by oversight activities like source data verification (not reported within 24 hours)	PDOTH01	Major	None
2	Unreported Special Situations detected by oversight activities like source data verification	PDOTH02	Minor	None
3	Entries in EDC or Source data either not available or incomplete for SDV in a timely manner	PDOTH03	Minor	None
	Withdrawal from study treatment/follow ups			
1	Subject withdrew from follow up but information was collected after withdrawal consent	PDWITH01	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
2	Subject withdrew from study treatment but continued receiving study treatment	PDWITH02	Major	Individual cases with potential impact on the primary endpoint might be excluded from PP (case review prior unblinding required)
	Observations detected but not classified as PD			
1	Subject with intake of forbidden Concomitant medication but patient withdrawal from study medication	TRACK01	NA	NA
2	Subject with incorrect entries for the randomisation factors at baseline	TRACK02	NA	NA
3	Subject randomized by mistake and never received the IMP	TRACK03	NA	NA

Appendix II: Calculation of planned dose

Protocol Number	Planned Dose
1, 1.1, 1.2 and country NE The Netherlands, Singapore, Spain	“Hemoglobin in g/dL” < 8: No dose “Hemoglobin in g/dL” > 15: No dose Visit 2 If "Serum pregnancy test" = "Positive": No dose 8 ≤ “Hemoglobin in g/dL” ≤ 14: 2 Kits 14 < “Hemoglobin in g/dL” ≤ 15: 1 Kit Visit 3 If "Serum pregnancy test" = "Positive": No dose “Weight in kg” < 70 and 8 ≤ “Hemoglobin in g/dL” < 10 and “ID persists” : 1 Kit “Weight in kg” < 70 and 10 ≤ “Hemoglobin in g/dL” ≤ 14 : No dose “Weight in kg” ≥ 70 and 8 ≤ “Hemoglobin in g/dL” < 10 and “ID persists” : 2 Kits “Weight in kg” ≥ 70 and 10 ≤ “Hemoglobin in g/dL” ≤ 14 and “ID persists” : 1 Kit “Hemoglobin in g/dL” > 14 : No dose Visit 4 and Visit 5 If "Serum pregnancy test" = "Positive": No dose “ID persists” : 1 Kit
2, 3 and country NE The Netherlands, Singapore, Spain	“Hemoglobin in g/dL” < 8: No dose “Hemoglobin in g/dL” > 15: No dose Visit 2 If "Serum pregnancy test" = "Positive": No dose 8 ≤ “Hemoglobin (from screening) in g/dL” ≤ 14: 2 Kits 14 < “Hemoglobin (from screening) in g/dL” ≤ 15: 1 Kit Visit 3 If "Serum pregnancy test" = "Positive": No dose “Weight in kg” < 70 and 8 ≤ “Hemoglobin (from screening) in g/dL” < 10 : 1 Kit “Weight in kg” < 70 and 10 ≤ “Hemoglobin (from screening) in g/dL” ≤ 14 : No dose “Weight in kg” ≥ 70 and 8 ≤ “Hemoglobin (from screening) in g/dL” < 10: 2 Kits “Weight in kg” ≥ 70 and 10 ≤ “Hemoglobin (from screening) in g/dL” ≤: 1 Kit “Hemoglobin in g/dL” > 14 : No dose Visit 4 and Visit 5 If "Serum pregnancy test" = "Positive": No dose “ID persists” : 1 Kit

Protocol Number	Planned Dose
If country = The Netherlands, Singapore, Spain	Same calculation as described above applies depending on protocol version. However, replace lower threshold for Hemoglobin by 10 g/dL instead of 8 g/dL.

Note:

ID is defined as serum ferritin <100 ng/mL, or 100 ng/mL ≤ serum ferritin ≤299 ng/mL if transferrin saturation (TSAT) is <20%. The laboratory and vital sign values closest to the injection date and time (<=) is used. In case no injection was done, the value closest to the visit date will be used.

Appendix III: Laboratory, vital signs and ECG parameters to be displayed

Category	Parameter	Unit	Number of decimal points (Min, Max)
Laboratory	Haemoglobin	g/dL	1
	Serum ferritin	ng/mL	1
	Transferrin saturation	%	1
	Phosphorus	mg/dL	1
	Creatinine	mg/dL	1
Vital Signs	Height	cm	1
	Weight	kg	1
	Systolic blood pressure	mmHg	0
	Diastolic blood pressure	mmHg	0
	Heart rate	beats/min	0
	Temperature	° C	1
	Pulse rate	beats/min	0

Appendix IV: Medications of special interest

Medication Category	Description	p=plain c=comb	ATC code (level)			ATC code details
			3rd	4th	5th	
ACE inhibitors	ACE inhibitors plain	p	C09A	A	all	
	ACE inhibitors combinations	c	C09B	A,B,X	all	A: ACEi and diuretics; B: ACEi and CCB; X: ACE and other
	Ramipril, statin and others	c	C10B	X	04,06	04: simvastatin, acetylsalicylic acid and ramipril ; 06: atorvastatin, acetylsalicylic acid and ramipril
	Lisinopril, statin and others	c	C10B	X	07	07: rosuvastatin, amlodipine and lisinopril
	Perindopril, statin and others	c	C10B	X	11,12,13,14,15	various combinations of perindopril and statin and amlodipine/acetylsalicylic acid/indapamide
Angiotensin II receptor blockers	ARBs plain	p	C09C	A	all	
	ARBs combinations	c	C09D	A,B	all	A: ARBs and diuretics; B: ARBs and CCB
	ARBs other combinations	c	C09D	X	01,02,03,05,06	various combinations of ARBs and others
	Rosuvastatin and valsartan	c	C10B	X	10	
Sacubitril-Valsartan (ARNI)	Valsartan and sacubitril	p	C09D	X	04	
Aldosterone Antagonists	Aldosterone-antagonists	p	C03D	A	all	
Beta-blocking agents	BB plain	p	C07A	A,B,G	all	A: non-selective; B: selective; G: alpha and beta
	BB and thiazides	c	C07B	A,B,G	all	A: non-selective and thiazides; B: selective and thiazides; G: alpha and beta and thiazides
	BB and other diuretics (excl. thiazides)	c	C07C	A,B,G	all	A: non-selective and other diurectis; B: selective and other diuretics; G: alpha and beta and other diuretics
	BB, thiazides, other diuretics	c	C07D	A,B	all	A: non-selective and thiazides and other diuretics; B: selective and thiazides and other diuretics
	BB and vasodilators	c	C07E	A,B	all	A: non-selective and vasodilators; B: selective and vasodilators
	BB, other combinations	c	C07F	B,X	all	B: BB and CCB, X: BB and other
	Perindopril and bisoprolol	c	C09B	X	02	
	Valsartan and nebivolol	c	C09D	X	05	

Medication Category	Description	p=plain c=comb	ATC code (level)			ATC code details
			3rd	4th	5th	
Digitalis Glycosides	Cardiac glycosides	p	C01A	A,B,C,X	all	A: Digitalis; B: Scilla; C: Strophanthus; X: Other cardiac
Loop diuretics	high-ceiling diuretics	p	C03C	all	all	A: Sulfonamides; B: Sulfonamides and potassium; C: Aryloxyacetic; D: Pyrazolone; X: others
	high-ceiling diuretics and potassium-sparing agents	c	C03E	B	all	
Thiazide and thiazide-like diuretics	low-ceiling diuretics, incl thiazide	both	C03A	all	all	
	other potassium-sparing agents	p	C03D	B	all	
	low-ceiling diuretics, excl thiazide	both	C03B	all	all	
	BB and thiazides	c	C07B	A,B	all	C03BB07 clofenamide and potassium
	ramipril, amlodipine and hydrochlorothiazide	c	C09B	X	03	
	Valsartan, amlodipine and hydrochlorthiazide	c	C09D	X	01, 03, 06	
	Aliskiren and hydrochlorothiazide	c	C09X	A	52, 54	
Ivabradine	Ivabradine plain	p	C01E	B	17	
	BB and ivabradine	c	C07F	X	05,06	X05: Ivabradine and Metoprolol; X06: Ivabradine and Carvedilol
Statin	HMG CoA reductase inhibitors	p	C10A	A	all	
	HMG CoA reductase inhibitors, combinations	c	C10B	all	all	
Acetsalicyl acid	Acetylsalicyl acid	p	B01A	C	06	
	HMG CoA reductase inhibitors, other combinations	c	C10B	X	01, 02, 04, 05, 06, 08, 12	

Medication Category	Description	p=plain c=comb	ATC code (level)			ATC code details
			3rd	4th	5th	
	Betablocking agents, other combinations	c	C07F	X	02, 03, 04	
Other antiplatelet drug	Platelet aggregation inhibitors	p	B01A	C	01-05, 07-11, 13, 15-19, 21-27	
Vitamin K antagonists	Vitamin K antagonists	p	B01A	A	all	
Direct thrombin inhibitors	Direct thrombin inhibitors	p	B01A	E	all	
Direct factor Xa inhibitors	Direct factor Xa inhibitors	p	B01A	F	all	

Note: ATC level 5 is not available for this study, Sponsor's representative will review all medications and categories defined by ATC level 5 will be based on this review.

Appendix V: KCCQ-12 Scoring

Four domain scores and 2 summary scores are generated from the KCCQ-12:

- Physical Limitation Score (KCCQ12-PL)
- Symptom Frequency Score (KCCQ12-SF)
- Quality of Life Score (KCCQ12-QL)
- Social Limitation Score (KCCQ12-SL)
- Overall Summary Score (KCCQ12)
- Clinical Summary Score (KCCQ12-C)

Scores are scaled 0-100, where 0 denotes the lowest reportable health status and 100 the highest.

Physical Limitation Score

The Physical Limitation score corresponds to Questions 1a, 1b and 1c. Responses are coded as follows:

Extremely limited..... 1

Quite a bit limited..... 2

Moderately limited..... 3

Slightly limited..... 4

Not at all limited..... 5

Limited for other reasons or did not do the activity.....6

A response of 6 is treated as a missing value for the purposes of scoring. If responses to two or more questions are missing, no score is computed. Otherwise, the score is then calculated by taking the average of the non-missing responses and rescaling to 0-100, as follows:

KCCQ12-PL = 100*[(average of Questions 1a, 1b and 1c) – 1]/4

Symptom Frequency Score

The Symptom Frequency score corresponds to Questions 2, 3, 4 and 5. Responses are coded as follows:

Question 2 Response

Every morning..... 1

3 or more times per week but not every day.....2

1-2 times per week..... 3

Less than once a week..... 4

Never over the past 2 weeks..... 5

Questions 3 and 4 Response

All of the time..... 1

Several times per day..... 2

At least once a day..... 3

3 or more times per week but not every day.....4

1-2 times per week..... 5

Less than once a week..... 6

Never over the past 2 weeks..... 7

Question 5 Response

Every night..... 1

3 or more times per week but not every day.....2

1-2 times per week..... 3

Less than once a week..... 4

Never over the past 2 weeks..... 5

If responses to three or more questions are missing, no score is computed. Otherwise, the score is then calculated by first rescaling each non-missing response to 0-100, then taking the average of the rescaled non-missing responses, as follows:

Q2 rescaled = 100 × (Q2 response – 1) ÷ 4

Q3 rescaled = 100 × (Q3 response – 1) ÷ 6

Q4 rescaled = 100 × (Q4 response – 1) ÷ 6

Q5 rescaled = 100 × (Q5 response – 1) ÷ 4

KCCQ12-SF = average of rescaled responses

Quality of Life Score

The Quality of Life score corresponds to Questions 6 and 7. Responses are coded as follows:

Question 6 Response

It has extremely limited my enjoyment of life.....1

It has limited my enjoyment of life quite a bit 2

It has moderately limited my enjoyment of life.....3

It has slightly limited my enjoyment of life.....4

It has not limited my enjoyment of life at all 5

Question 7 Response

Not at all satisfied..... 1

Mostly dissatisfied..... 2

Somewhat satisfied..... 3

Mostly satisfied..... 4

Completely satisfied..... 5

If responses to both questions are missing, no score is computed. Otherwise, the score is calculated by taking the average of the non-missing responses and rescaling to 0-100, as follows:

KCCQ12-QL = 100*[(average of Questions 6 and 7) – 1]/4

Social Limitation Score

The Social Limitation score corresponds to Questions 8a, 8b and 8c. Responses are coded as follows:

Severely limited..... 1

Limited quite a bit..... 2

Moderately limited..... 3

Slightly limited..... 4

Did not limit at all..... 5

Does not apply or did not do for other reasons.....6

A response of 6 is treated as a missing value for the purposes of scoring. If responses to two or more questions are missing, no score is computed. Otherwise, the score is then calculated by taking the average of the non-missing responses and rescaling to 0-100, as follows:

KCCQ12-SL = 100*[(average of Questions 8a, 8b and 8c) – 1]/4

Overall Summary Score

The Summary score represents an integration of the subject's physical limitation, symptom frequency, quality of life and social limitation. If all four domain scores are missing, no summary score is computed. Otherwise, the score is calculated as the average of the non-missing domain scores:

KCCQ12 = average of KCCQ12-PL, KCCQ12-SF, KCCQ12-QL and KCCQ12-SL

Clinical Summary Score

The clinical summary score represents an integration of the subject's physical limitation and symptom frequency. If both domain scores are missing, no clinical summary score is computed. Otherwise, the score is calculated as the average of the non-missing domain scores:

KCCQ12-C = average of KCCQ12-PL and KCCQ12-SF

Appendix VI: EQ-5D Scoring

The health states are described in terms of five digit numbers based on the answers to each of the five questions. The states can then be converted to a single score using a choice-based method (e.g. time trade–off (TTO)) as shown in Table 8.

In the present study, the country-specific scorings for the UK will be used [11].

Table 8 Scoring of the EQ-5D-5L Based on UK TTO Values

	Central estimate[a]	Value for health state 23245
Constant	1.000	1.000
Mobility		
Slight	0.058	0.058
Moderate	0.076	
Severe	0.207	
Unable	0.274	
Self-care		
Slight	0.050	
Moderate	0.080	0.080
Severe	0.164	
Unable	0.203	
Usual activities		
Slight	0.050	0.050
Moderate	0.063	
Severe	0.162	
Unable	0.184	
Pain/discomfort		
Slight	0.063	
Moderate	0.084	
Severe	0.276	0.276
Extreme	0.335	
Anxiety/depression		
Slight	0.078	
Moderate	0.104	
Severe	0.285	
Extreme	0.289	0.289
The value for health state 23245	$1 - (0.058 + 0.080 + 0.050 + 0.276 + 0.289)$	$= 0.247$

CODA results from final model available from the authors upon request.

[a]Note that the coefficients reported here are the mean coefficients from the Bayesian regressions.

The questionnaire also contains a visual analogue scale (VAS) for the subjects to rate their current health state. The VAS ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).