This supplement contains the following items:

1. Original protocol, final protocol, and a summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, and a summary of changes.

LUITPOLD PHARMACEUTICALS, INC.

PROTOCOL

No. 1VIT15043

IND #: 127910

A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Injectafer® (Ferric Carboxymaltose) as Treatment for Heart Failure with Iron Deficiency

SPONSOR

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SIGNATURES OF AGREEMENT FOR PROTOCOL

Study Synopsis

Protocol No. 1VIT15043

Title:	**A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Injectafer® (Ferric Carboxymaltose) as** Treatment for Heart Failure with Iron Deficiency
Study Drug:	Ferric Carboxymaltose (Injectafer®)
Objective:	The primary objective of this study is to determine the efficacy and safety of iron therapy using intravenous (IV) ferric carboxymaltose (FCM), relative to placebo, in the treatment of participants in heart failure with a reduced ejection fraction and with iron deficiency.
Design:	This is a double-blind, multicenter, prospective, randomized, placebo-controlled study to assess the effects of IV FCM compared to placebo on the 12-month rate of death, hospitalization for worsening heart failure, and the 6-month change in 6 minute walk test (6MWT) for patients in heart failure with iron deficiency. After an initial screening period of up to 28 days, eligible participants will be stratified by region and randomized in a 1:1 ratio to FCM or placebo for treatment. Study drug administration will occur on Day 0 and Day 7 (± 2) as an undiluted slow IV push, with additional study visits planned at 3 month intervals, and additional dosing administered every 6 months as applicable (based on dose regimen below). In a subset of sites, all participants will return for recurrent laboratory assessment (chemistry, hematology and iron indices) at Day 21 ($\pm$ 7) after each course of investigational treatment. For all participants, hematology, ferritin, and transferrin saturation (TSAT), with appropriate safety evaluations, to determine additional treatment, will occur at 6 month intervals.

Inclusion Criteria:

1. Adult (≥18 years of age) able to provide informed consent.
2. Stable heart failure (NYHA II-IV) on maximally-tolerated background therapy (as determined by the site Principle Investigator) for at least 4 weeks with no dose changes in heart failure drugs during the last 2 weeks.
3. Able and willing to perform a 6MWT at the time of randomization.
4. Reduced left ventricular ejection fraction. Assessment must be performed at least 12 weeks after major cardiac surgical intervention including coronary artery bypass graft (CABG), valvular repair/replacement, or cardiac resynchronization therapy (CRT) device implantation.

a. Left ventricular ejection fraction ≤35% obtained during the screening visit OR either of the following
    i. Historical value of ejection fraction ≤35% within 12 months of screening visit
    ii. Historical value of ejection fraction ≤25% within 24 months of screening visit

5. Hemoglobin >9.0 g/dL and <13.5 g/dL (females) or <15.0 g/dL (males).
6. Serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%.
7. Either documented hospitalization for heart failure within 12 months of enrollment or screening visit N-terminal-pro-brain natriuretic peptide (NT-proBNP) >600 pg/ml (or BNP >200 pg/mL) for patients with normal sinus rhythm or NT-proBNP >1000 pg/ml (or BNP >400 pg/mL) for patients with atrial fibrillation. *NOTE: NT-proBNP must be used to confirm eligibility for patients taking sacubitril/valsartan.*

Exclusion Criteria:

1. Current or planned oral iron supplementation. Iron-containing multivitamins (<30 mgs /day) are permitted.
2. Known hypersensitivity reaction to any component of FCM.
3. History of acquired iron overload, or the recent receipt (within 3 months) of erythropoietin stimulating agent, IV iron therapy, or blood transfusion.
4. Acute myocardial infarction, acute coronary syndrome, transient ischemic attack, or stroke within 3 months of enrollment.
5. Uncorrected severe aortic stenosis, severe valvular regurgitation, or left ventricular outflow obstruction requiring intervention.
6. Current atrial fibrillation or atrial flutter with a mean ventricular response rate >100 per minute (at rest).
7. Current or planned mechanical circulatory support or heart transplantation.
8. Hemodialysis or peritoneal dialysis (current or planned within the next 6 months).
9. Documented liver disease, or active hepatitis (i.e. alanine transaminase or aspartate transaminase >3 times the upper limit of normal range).
10. Current or recent (within 3 years) malignancy with exception of basal cell carcinoma or squamous cell carcinoma of the skin, or cervical intraepithelial neoplasia.
11. Known gastrointestinal bleeding. Patients with screening ferritin <15ng/ml must have an appropriate evaluation within 3 months of screening.
12. Female participant of child-bearing potential who is pregnant, lactating, or not willing to use adequate contraceptive precautions during the study and for up to 5 days after the last scheduled dose of study medication.
13. Inability to return for follow up visits within the necessary windows

Study Drug Administration	Initial treatment will occur on Day 0 (date of randomization) and Day 7. On Day 0 and Day 7, Group A (FCM) will receive a 750 mg undiluted blinded dose of IV FCM at the rate of approximately 100 mg (2 mL)/minute; Group B (placebo) will receive a blinded placebo (15 cc of normal saline) IV push at 2 mL/minute. Participants in Group A with body weight <50 kg (110 pounds) will have individual FCM doses adjusted to 15 mg/kg, not to exceed an individual dose of 750 mg, or a cumulative dose of 1500 mg per treatment cycle. All participants will be dosed every 6 months for the duration of the trial. Participants randomized to the FCM arm will be dosed as indicated based on hemoglobin (Hgb) levels (i.e. Hgb <13.5 g/dl [females] or <15.0 g/dl [males]]) and iron studies (i.e. serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%). Participants not meeting post- randomization lab criteria for blood counts and iron studies and all participants randomized to the placebo arm will be administered IV placebo at each visit. Unblinded site personnel, responsible for preparation and administration of the FCM or Placebo, will ensure that the participant and all blinded site staff are not able to observe the preparation or administration of study treatment.
Patient Assessments	Efficacy and Safety Follow-up: All participants will be followed from the time of randomization until completion of the trial. The last participant randomized will be followed for 12 months. After treatment on Day 0 and Day 7, participants will be evaluated at 3 month intervals (in person or via telephone), with additional dosing administered every 6 months as applicable (based on dose regimen below). In a subset of sites, all participants will return for recurrent laboratory assessment (chemistry, hematology, and iron indices) at Day 21 ($\pm$ 7) after each course of investigational treatment. Hematology, ferritin, and transferrin saturation (TSAT) laboratory assessments will be performed in all participants, with appropriate safety evaluations, to determine if additional treatment will occur at 6 month intervals. At the conclusion of the study all participants will be assessed for the occurrence of any potential endpoint or serious adverse events. Attempts to determine Vital Status, including endpoint ascertainment, for participants who are lost to follow-up or withdrawn will be made via a search of available public records, and other appropriate investigative techniques, including the potential use of third party vendors as described in the informed consent form and in accordance with applicable regulatory requirements.
Primary Endpoint:	Hierarchical composite of 1) death, 2) hospitalization for heart failure (as defined in section 10.2), or 3) change in 6MWT. (Death and hospitalizations for heart failure will be evaluated at one year, Change in 6MWT will be evaluated at 6 months) and tested using the nonparametric Wilcoxon-type test.

Secondary Endpoints

1. Time to first event of the composite of cardiovascular death or heart failure hospitalization. The composite endpoint will be composed of adjudicated occurrence (as defined in section 10.2) of one of the following:

   a. Cardiovascular Death
      i. Death due to Heart Failure
      ii. Death due to Acute Myocardial Infarction
      iii. Sudden Cardiac Death
      iv. Death due to Stroke
      v. Death due to other Cardiovascular Causes
   b. Hospitalization for Worsening Heart Failure

2. Mean change in 6MWT from baseline to 12 months
3. Time to first event of the composite of cardiovascular death or intervention for worsening heart failure (hospitalization or urgent heart failure visits)
4. Time to first event of the composite of cardiovascular death and cardiovascular hospitalizations
5. Time to cardiovascular death

Additional events to be adjudicated for analysis of the secondary endpoints include:

a) Non-cardiovascular death
b) Hospitalization for myocardial infarction
c) Hospitalization for stroke
d) Other cardiovascular hospitalizations
e) Urgent heart failure visits

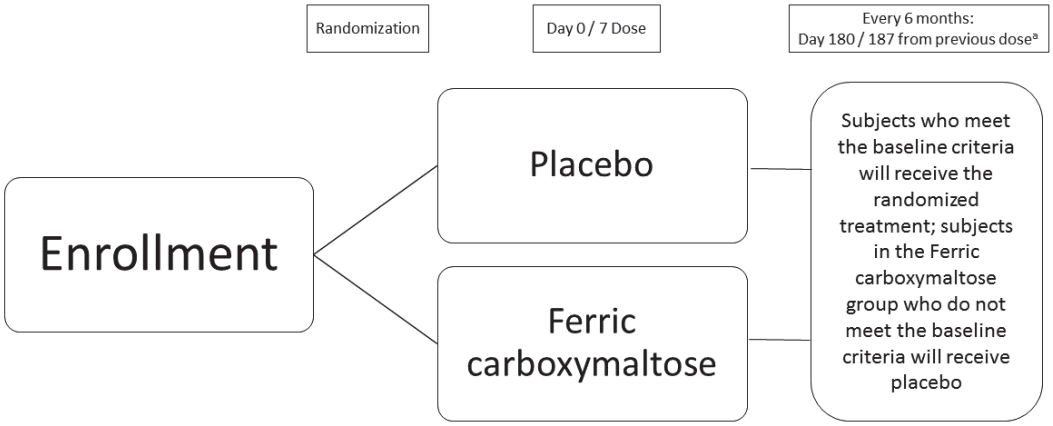
All events are operationally defined in Section 10.2. Events will be confirmed by the Clinical Events Classification (CEC) Committee of the Duke Clinical Research Institute (DCRI)

Study duration per participant: Screening Phase: up to 28 days prior to randomization.
Post randomization phase: Variable with a minimum of 365 Days.

Study Sites: Approximately 200

Participant Number: Approximately 3014

Figure 1. Study Diagram



[a] All participants will be dosed every 180 and 187 days from their previous dose for the entire study duration. Randomized treatment will be administered if hemoglobin <13.5 g/dl (females) or <15.0 g/dl (males) and serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%; placebo will be administered to participants in the Ferric carboxymaltose group who do not meet the above criteria.

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LIST OF ABBREVIATIONS

6MWT	Six Minute Walk Test
AE	Adverse event
ALT	Alanine Aminotransferase
AST	Aspartate aminotransferase
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
BUN	Blood urea nitrogen
CABG	Coronary Artery Bypass Grafting
cc	cubic centimeter
CEC	Clinical Events Classification
CFR	Code of Federal Regulations
CI	Confidence Interval
CKD	Chronic Kidney Disease
CK-MB	Creatine Kinase-Myocardial Band
cm	Centimeter
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CV	Cardiovascular
DCRI	Duke Clinical Research Institute
dL	Deciliter
DSMB	Data and Safety Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
e.g.	For example
EOS	End of Study
EU	European Union
FCM	Ferric Carboxymaltose
FDA	Food and Drug Administration
Fe	Iron
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
Hct	Hematocrit
HF	Heart Failure
Hg	Mercury
Hgb	Hemoglobin
ICD	Implantable Cardioverter-Defibrillator
ICH	International Conference on Harmonisation
i.e.	that is
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
IRT	Interactive Response Technology
ITT	Intention to Treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
Kg	Kilogram
L	Liter

LBBB	Left Bundle-Branch Block
LDH	Lactic dehydrogenase
LVEF	Left Ventricular Ejection Fraction
LVOT	Left Ventricular Outflow Tract
MB	Myocardial b Fraction
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
m	Meter
mg	Milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial Infarction
mL	Milliliter
ng	Nanogram
NS	Normal Saline
NT-proBNP	N-Terminal Prohormone of Brain Natriuretic Peptide
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
pg	Picogram
PGA	Patient Global Assessment
PTH	Parathyroid Hormone
RBC	Red blood cell
RDW	Red (cell) distribution width
SAE	Serious Adverse Event
SC	Steering Committee
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
TVI	Time Velocity Integral
ULN	Upper Limit of the Normal
US	United States
USP	United States Pharmacopeia
UK	United Kingdom
WBC	White Blood Cell
w/v	weight / volume

1.0 INTRODUCTION

1.1 Heart Failure with Iron Deficiency

Over 5 million people in the United States (US) live with heart failure. Epidemiological studies in heart failure suggest a 50% prevalence of either absolute iron deficiency, defined as serum ferritin <100 ng/mL, or functional iron deficiency, defined as a ferritin 100 to 300 ng/mL with transferrin saturation (TSAT) <20% [**van Veldhuisen 2011; Ebner 2013**]. The prevalence of iron deficiency increases with the severity of heart failure and etiologies include insufficient dietary iron, poor iron absorption, gastrointestinal blood loss, chronic disease, and repeated blood sampling for ongoing medical evaluation of heart failure and comorbid conditions.

Alteration in iron homeostasis has been identified as an independent risk factor for mortality in patients with heart failure [**Okonko 2011**; **Jankowska 2013**]. It is hypothesized that reduced oxygenation, combined with insufficient iron for appropriate oxygen transportation and storage, may have additive untoward effects on oxidative metabolism and cellular immune mechanisms in this population. Iron deficiency may also increase the risk of thrombosis and mortality among patients in heart failure with iron deficiency [**Streja 2008**].

1.2 Treatment of Iron Deficiency in Heart Failure

Evidence in support of the therapeutic value of intravenous (IV) iron repletion with ferric carboxymaltose (FCM) for patients in heart failure with a reduced ejection fraction and iron deficiency is provided by 4 European studies: FER-CARS-01, FER-CARS-02 (FAIR-HF), FER-CARS-03 (EFFICACY-HF), and FER-CARS-05 (CONFIRM-HF). In addition to measures of iron repletion and hemoglobin changes, these studies focused on changes from baseline in New York Heart Association (NYHA) functional class, Patient Global Assessment (PGA), and the 6-minute walk test (6MWT).

In the most recent of the studies, CONFIRM HF, a total of 301 participants (150 FCM, 151 placebo) were treated for up to 52 weeks (longest duration among the 4 studies). The primary efficacy analysis confirmed the benefit of FCM relative to placebo for the improvement in 6MWT distance at Week 24, with a comparative difference (FCM versus placebo) in the change from baseline reported as least squares mean (± standard error) of 33.2 ± 10.52 m (p=0.002). The treatment benefit of FCM versus placebo in 6MWT distance was sustained through to Week 52 ($p \leq 0.001$) and was consistent across subgroups. Commensurate with the improvement in 6MWT distance, improvements in PGA, NYHA functional class, overall Kansas City Cardiomyopathy Questionnaire (KCCQ) score, and fatigue score were seen in FCM-treated participants as compared to placebo-treated participants. Treatment with FCM versus placebo was also associated with a significant reduction in the risk of hospitalization due to worsening heart failure (hazard ratio: 0.40; 95% confidence interval [CI]: 0.2 to 0.8; p=0.009) and a significant reduction in the risk of first hospitalization due to worsening heart failure or all-cause death (hazard ratio: 0.53; 95% CI: 0.30 to 0.95; p = 0.03). Similar trends for reduction in hospitalization were reported for FCM and iron sucrose [**Kapoor 2013**].

A meta-analysis of these four trials was conducted to assess the association of FCM exposure with morbidity and mortality [**Anker 2015**]. The analysis included individual participant pooled data for 839 participants, 504 of whom with FCM exposure versus 335 with placebo exposure. The primary endpoint was defined as the composite outcome of cardiovascular death and cardiovascular hospitalization. Participants randomized to FCM had a lower rate of cardiovascular death and cardiovascular hospitalization compared to placebo, with a rate ratio of 0.59 (95% CI: 0.40 to 0.88; p=0.009) in a recurrent events analysis. Additionally, exposure to

FCM was associated with reduced cardiovascular death and hospitalization for heart failure, with a rate ratio of 0.53 (95% CI: 0.33 to 0.86; p=0.011) and all-cause death and cardiovascular hospitalization, with a rate ratio of 0.60 (95% CI: 0.41 to 0.88; p=0.009).

The four European trials, together with the meta-analysis, suggest that IV iron repletion as treatment for patients in reduced left ventricular ejection fraction with iron deficiency is associated with improvement in functional health (the 6MWT), patient-reported outcomes, morbidity defined as cardiovascular hospitalization, and mortality. Given that FCM is approved by the US Food and Drug Administration (FDA) for use in iron-deficiency anemia [US Package Insert], a clinical development program is proposed seeking FDA approval for FCM as treatment for patients in heart failure with reduced ejection fraction who have iron deficiency.

1.3 Injectafer® (Ferric Carboxymaltose)

1.3.1 Key Features of Ferric Carboxymaltose

Injectafer® (FCM) is a stable Type I polynuclear iron (III)-hydroxide carbohydrate complex developed as an IV iron replacement therapy for the treatment of iron deficiency anemia. After IV administration, FCM is mainly found in the reticuloendothelial system which includes the liver, spleen, and bone marrow. The iron slowly dissociates from the complex and can be efficiently used in the bone marrow for hemoglobin synthesis. The carbohydrate moiety of FCM is metabolized by the glycolytic pathway. FCM is approved for the treatment of iron deficient anemia, and is an investigational product in this study for patients in heart failure with iron deficiency.

1.3.2 Injectafer® versus Other Parenteral Iron Agents

There is considerable efficacy and safety experience with the various available parenteral iron preparations. However, prior to the approval of non-dextran formulations, the risk of systemic adverse reactions restricted IV iron use. The use of FCM offers significant advantages compared to other available IV iron preparations. Due to its structure, Injectafer® is more stable than iron gluconate and iron sucrose resulting in a slow delivery of the complexed iron to endogenous iron binding sites. In animals, FCM has approximately $1/5^{th}$ the acute toxicity that has been reported for iron sucrose. These characteristics of FCM make it possible to administer much higher single doses over shorter periods of time than iron gluconate or iron sucrose, resulting in fewer administrations to replenish iron stores, and convenient outpatient use. In the EU, ferumoxytol has been withdrawn from use and in the US, it has been given a black box warning.

1.3.3 Injectafer® Human Experience

The Injectafer® clinical development program demonstrated the effectiveness and safety of Injectafer® in the treatment of iron-deficiency anemia. The drug is approved for the treatment of iron deficiency anemia in adult populations who have intolerance to oral iron, have had unsatisfactory responses to oral iron, or who have non-dialysis dependent CKD. Clinical data are currently available from 20 Phase 2 and 3 studies including 5,799 patients, with iron deficient anemia or iron deficiency anemia associated with CKD who received Injectafer®

A clinical pharmacokinetic study (VIT-IV-CL-001) using positron emission tomography demonstrated a fast initial elimination of radioactively labeled iron (Fe) $^{52}Fe/^{59}Fe$ Injectafer (FCM) from the blood, with rapid transfer to the bone marrow and rapid deposition in the liver and spleen. Eight hours after administration, 5 to 20% of the injected amount of radioactively-labeled Fe was still detected in the blood.

Important details of pre-clinical safety and efficacy and clinical safety and efficacy can be found in the Investigator's Brochure. Ferric carboxymaltose received approval from the United Kingdom (UK) Medicines and Healthcare Products Regulatory Agency (MHRA) on June 15, 2007 (EU Trade name: Ferinject). Injectafer® now has marketing authorization in 70 countries, and is currently marketed in 61 of these countries. Injectafer® received approval for the treatment of iron-deficiency anemia from the US (FDA) on July 25, 2013.

2.0 TRIAL OBJECTIVE

2.1 Primary Objective

To determine the efficacy and safety of iron therapy using intravenous (IV) FCM, relative to placebo, in the treatment of patients in heart failure with reduced ejection fraction and with iron deficiency.

2.2 Secondary Objective

To evaluate the effect of IV FCM, relative to placebo, on the functional capacity of patients in heart failure with reduced ejection fraction and with iron deficiency.

3.0 OVERALL STUDY DESIGN AND RATIONALE

3.1 Overall Study Design

This is a double-blind, multicenter, prospective, randomized, placebo-controlled study to assess the effects of IV FCM compared to placebo on the 12-month rate of death and hospitalization for worsening heart failure, and change in 6MWT at 6 month for patients in heart failure with reduced ejection fraction and with iron deficiency.

After an initial screening period of up to 28 days, eligible participants will be stratified by region and randomized in a 1:1 ratio to FCM or placebo. Study drug administration will occur on Day 0 and Day 7 as an undiluted slow IV push, with additional study visits (in person or via telephone) planned at 3 month intervals, and additional dosing administered every 6 months as applicable (based on dose regimen below). In a subset of sites, all participants will return for recurrent laboratory assessment (chemistry, hematology, and iron indices) at Day 21 ($\pm$ 7) after each course of investigational treatment. For all participants, hematology, ferritin and transferrin saturation (TSAT), with appropriate safety evaluations, to determine additional treatment, will occur at 6 month intervals.

Initial treatment will occur on Day 0 and Day 7. On Day 0 and 7, Group A (FCM) will receive a 750 mg undiluted, blinded dose of IV FCM at the rate of approximately 100 mg (2 mL)/minute; Group B (placebo) will receive a blinded placebo (15 cc of normal saline) IV push at 2 mL/minute. Participants in Group A with body weight <50 kg (110 pounds) will have individual FCM doses adjusted to 15 mg/kg, not to exceed an individual dose of 750 mgs or a cumulative dose of 1500 mg per treatment cycle.

All participants randomized will be dosed every 6 months. Participants randomized to the FCM arm will be dosed as indicated based on hemoglobin levels (i.e. Hgb <13.5 g/dl [females] or <15.0 g/dl [males)]) and iron studies (i.e. serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%). Participants not meeting pre-specified laboratory criteria for blood counts and iron studies

and all participants randomized to the placebo arm will be administered IV placebo infusion at each visit.

Unblinded site personnel, responsible for preparation and administration of the FCM or Placebo, will ensure that the participant and all blinded site staff are not able to observe the preparation or administration of study treatment.

3.2 Rationale of Study Design and Choice of Control Groups

Since FCM is being studied as a treatment for heart failure patients with a reduced ejection fraction and comorbid iron deficiency, it is important to establish its efficacy and safety in terms of clinically significant endpoints including cardiovascular morbidity.

This study will assess the efficacy and safety of FCM as a treatment for participants in heart failure with reduced ejection fraction and concomitant iron deficiency by comparing the proposed regimen to placebo (normal saline). The placebo arm is justified as participants will be maintained on the maximally tolerated background therapy for heart failure with a reduced ejection fraction.

3.3 Schedule of Events

Study Procedures	Screening	Treatment Phase		Follow-up Phase						
				Select Sites only					Select Sites only	
Days	**-28 to -1**	**0**	**7±2**	**21 ±7[a,k]**	**90 ±14[a,b,l]**	**160-178 [a,b]**	**180±7 [a,b]**	**187 ±7 [a,b]**	**201 ±7[a,k]**	**EOS[c]**
Informed consent	X									
Inclusion/exclusion criteria	X	X[j]								
Demographics	X									
Targeted medical history	X									
Targeted Physical Exam		X[j]								X
Vital signs		X[d]	X[d]				X[d]	X[d]		X
Height (cm) & weight (kg)[e]		X[j]					X			
Urine pregnancy test[f]		X[j]					X			X
Vitamin D and PTH[k]		X								
Left ventricular ejection fraction	X[g]									
Randomization[n]		X								
Hematology laboratory[h]	X	X		X		X			X	X
Chemistry laboratory[h]		X		X		X			X	X
Iron indices[h]	X	X		X		X			X	X
6 Minute Walk Test		X[j]					X[m]			
NT-proBNP[h]	X	X					X			X
Serious Adverse Event reporting		X	X		X	X	X	X		X
Concomitant medications	X	X	X				X	X		X
IV FCM/ IV Placebo[n]		X	X				X[i]	X[i]		

Abbreviations: EOS = End of Study; FCM = ferric carboxymaltose; IV = intravenous; NT-proBNP = N-terminal pro-brain natriuretic peptide; PTH = Parathyroid Hormone;

a Visits will be repeated every 180 days for the duration of the study
b Visit should not be performed if it would occur within 30 days of the EOS visit.
c EOS visit for all participants will be scheduled once the last participant has reached 6 months on study and the anticipated number of outcome events (section 8) reaches 840.
d On study drug dosing days vital signs will be collected predose, immediately postdose, and 30 minutes postdose.
e Height assessed at Day 0 only; weight assessed at Day 0 and prior to each dosing cycle.
f. Females of childbearing potential
g. Historical value can be used if performed within 12 months of screening visit (or 24 months if LVEF ≤25%), must be performed at least 12 weeks after major cardiac intervention-including CABG, valvular intervention, or cardiac resynchronization therapy device implantation.
h. Screening laboratory measures may be performed locally all other visits will be analyzed through a central laboratory

i All participants randomized will be dosed every 6 months. Participants randomized to the FCM arm will be dosed as indicated based on blood counts (i.e. Hgb <13.5 g/dL [females] or <15.0 g/dL [males)]) and iron studies (i.e. serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%). Participants not meeting pre-specified laboratory criteria for blood counts and iron studies and all participants randomized to the placebo arm will be administered IV placebo infusion at each visit. The second of the 2 dosing visits should occur at Day 7±2 after the first dose.

j. Prior to randomization

k Only for participants at select sites performing additional chemistry labs on Day 21 (±7) post dosing.

l. May be performed via telephone or in person.

m. Performed at Day 180 and Day 360 visits only.

n. To be performed by unblinded site personnel. All other procedures must be performed by personnel blinded to the treatment assignment

4.0 PARTICIPANT SELECTION

4.1 Number and Type of Participants

The study cohort will comprise approximately 3,014 participants in heart failure with iron deficiency who fulfill the inclusion criteria, do not meet any of the exclusion criteria, and who have given written informed consent.

4.2 Screening Phase

Once a participant signs the informed consent document and enters the screening phase, a unique screening number will be assigned via an interactive response technology (IRT) system.

4.2.1 Inclusion Criteria

1. Adult (≥18 years of age) able to provide informed consent
2. Stable heart failure (NYHA II-IV) on maximally-tolerated background therapy (as determined by the site principle investigator) for at least 4 weeks with no dose changes in heart failure drugs during the last 2 weeks.
3. Able and willing to perform a 6MWT at the time of randomization.
4. Reduced left ventricular ejection fraction. Assessment must be performed at least 12 weeks after major cardiac surgical intervention including coronary artery bypass graft (CABG), valvular repair/replacement, or cardiac resynchronization therapy (CRT) device implantation.
    a. Left ventricular ejection fraction ≤35% obtained during the screening visit OR either of the following
        i. Historical value of ejection fraction ≤35% within 12 months of screening visit
        ii. Historical value of ejection fraction ≤25% within 24 months of screening visit
5. Hemoglobin >9.0 g/dl and <13.5 g/dl (females) or <15.0 g/dl (males)
6. Serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%.
7. Either documented hospitalization for heart failure within 12 months of enrollment OR screening visit N-terminal-pro-brain natriuretic peptide (NT-proBNP) > 600 pg/ml (or BNP > 200 pg/mL) for patients with normal sinus rhythm or >1000 pg/ml (or BNP > 400 pg/mL) for patients with normal sinus rhythm or >1000 pg/ml for patients with atrial fibrillation. NOTE: *NT-proBNP must be used to confirm eligibility for patients taking sacubitril/valsartan.*

4.2.2 Exclusion Criteria

1. Current or planned oral iron supplementation. Iron-containing multivitamins (< 30 mgs /day) are permitted.
2. Known hypersensitivity reaction to any component of FCM.
3. History of acquired iron overload, or the recent receipt (within 3 months) of erythropoietin stimulating agent, IV iron therapy, or blood transfusion.
4. Acute myocardial infarction, acute coronary syndrome, transient ischemic attack, or stroke within 3 months of enrollment.
5. Uncorrected severe aortic stenosis, severe valvular regurgitation, or left ventricular outflow obstruction requiring intervention.
6. Current atrial fibrillation or atrial flutter with a mean ventricular response rate >100 per minute (at rest).
7. Current or planned mechanical circulatory support or heart transplantation.
8. Hemodialysis or peritoneal dialysis (current or planned within the next 6 months).
9. Documented liver disease or active hepatitis (i.e. alanine transaminase or aspartate transaminase >3 times the upper limit of normal range).
10. Current or recent (within 3 years) malignancy with exception of basal cell carcinoma or squamous cell carcinoma of the skin, or cervical intraepithelial neoplasia.
11. Known gastrointestinal bleeding. Patients with screening ferritin <15 ng/ml must have an appropriate evaluation within 3 months of screening.
12. Female participants of child-bearing potential who is pregnant, lactating, or not willing to use adequate contraceptive precautions during the study and for up to 5 days after the last scheduled dose of study medication.
13. Inability to return for follow up visits within the necessary windows

4.3 Participant Assignment and Randomization Process

Participants who meet all inclusion requirements and no exclusionary criteria will be offered enrollment in this study. Enrolled participants will be stratified by region and randomized in a 1:1 ratio to receive either IV FCM or IV Placebo.

The FCM Group will initially receive 2 blinded doses of FCM at 15 mg/kg to a maximum of 750 mg per dose for a maximum total dose of 1500 mg.

The Placebo Group will receive 2 blinded doses of 15 mL of normal saline.

Participants and blinded study staff will remain blinded to the treatment assignment for the duration of the study.

4.4 Withdrawal from Study

Any participant who wishes to withdraw from the study may do so at any time without the need to justify their decision. The investigator may withdraw a participant from active study treatment at any time if it is felt to be in the best interest of the participant

At time of withdrawal from the study, procedures for the EOS visit must be immediately performed regardless of whether the participant has completed study drug treatment. Information collected previously as part of the study will be retained unless the patient specifically withdraws consent, in writing. The participant should be contacted at the end of the study to assess for the occurrence of any potential endpoint events. Additionally, if the participant cannot be contacted, attempts to determine the Vital Status will be performed via a search of available public records, third party vendor search, medical record review, additional contacts provided by the patient, and other appropriate investigative techniques as described in the informed consent form and in accordance with applicable regulatory requirements.

In event of site closure, participants will be asked to agree to follow up at another research site, if available, or for follow up by via a patient follow -up group.

4.5 Discontinuation from Study Drug

Participants may elect to discontinue study drug, but wish to remain in the study for follow-up. In those situations, patients will be asked to continue the normal clinical trial schedule for ascertainment of endpoint and safety events.

If a participant permanently discontinues investigational product and is unable to attend visits in-person, he/she will be contacted by telephone, or other methods to assess study outcomes and vital status, unless the participant has specifically withdrawn consent for all forms of contact. Every effort should be made to educate the participants on the importance of remaining in the study and attending scheduled study visits including those required after early discontinuation of investigational product. Other participant follow-up options to collect study outcomes and vital status should be pursued according to local laws and regulations. If one of these alternate methods to collect study outcomes and vital status is acceptable to the participant, then the participant will be deemed not to have withdrawn consent for follow-up.

4.6 Participants Deemed Lost to Follow-up

Investigators should make every effort to contact participants who are deemed lost to follow-up and who have not withdrawn consent to follow-up contacts, including medical record review, pursuing any alternative contact methods permitted by local regulations. Where permitted, a third party may be used to locate alternative participant contact information that will be provided to the investigator. All attempts to contact participants will be documented in the participant's source notes.

Should a participant fail to attend the clinic for a required study visit, the site should attempt to contact the participant and re-schedule the missed visit as soon as possible. The site should also counsel the participant on the importance of maintaining the assigned visit schedule. In cases where the participant does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the participant. Should the participant continue to be unreachable, then and only then, will he/she be considered "Lost to

Follow-up." Nonetheless, efforts to attempt to locate and contact the participant, and to ascertain the participant's vital status will continue until trial completion.

4.7 Concomitant Intervention

Concomitant intervention is defined as follows:

- Blood transfusion.
- Use of IV iron outside of protocol.

When concomitant intervention occurs, the date of the intervening event should be recorded in the source documents, and the eCase Report Form (eCRF). The participant should continue in the study as scheduled.

5.0 STUDY DRUG

5.1 Formulation, Packaging and Storage

All investigational medication to be used in this study [supplied by Luitpold Pharmaceuticals, Inc.] will have been prepared according to Good Manufacturing Practices (GMP).

FCM (trade name, Injectafer®) will be supplied as 15 ml vials, containing 750 mg of iron as 5% w/v iron containing a polynuclear iron(III)-hydroxide 4(R)–(poly-(1-->4)-*O* α -D-glucopyranosyl)-oxy-2 (R), 3(S), 5(R), 6-tetrahydroxy-hexonate complex in a solution of water for injection [50 mg/ml] and will be labeled according to FDA investigational regulatory requirements.

Placebo (normal saline) will be supplied as 15 ml vials.

All IV study drugs (FCM and Normal Saline) must be kept in a secure place at the investigational site, and stored at room temperature (see USP). The study medication should not be frozen. Vials may not be used for more than 1 dose, or for more than 1 participant. All vials (used and unused) should be kept by the study staff for reconciliation by the monitor. Following reconciliation, sites may destroy used and unused study drug on site using local procedures, provided a drug destruction policy is in place, or it may be returned to Luitpold Pharmaceuticals, Inc.

5.2 Drug Administration/Regimen

The Principal Investigator or designee will supervise administration of the study drug to participants. The participants should remain blinded to the identity of the study drug for the duration of the trial.

Group A: Group A (FCM) will receive a 750 mg undiluted blinded dose of IV FCM at the rate of approximately 100 mg (2 mL)/minute on Day 0 and Day 7; Participants in Group A with body weight <50 kg (110 pounds) will have individual FCM doses adjusted to 15 mg/kg, not to exceed an individual dose of 750 mg or a cumulative dose of 1500 mg per treatment cycle.

Group B: Group B (placebo) will receive a blinded placebo (15 cc of normal saline) IV push at 2 mL/minute on Day 0 and Day 7.

All participants will be dosed every 6 months. At each 6-month interval, 2 doses of study drug will be administered as described above for Day 0 and Day 7. The same randomized treatment will be administered if Hgb <13.5 g/dL (females) or <15.0 g/dL (males) and serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%; placebo will be administered to participants in the FCM group who do not meet the above criteria.

Site personnel will ensure the participant and blinded study staff are not able to observe the preparation or administration of study treatment injections.

5.3 IV Medication Precautions

When administering FCM or Placebo, the following precautions will be taken:

- The participant will be evaluated clinically prior to drug administration to assess the development of clinically significant conditions.
- The vials will be visually inspected for particulate matter and discoloration before use. If noted, the vial will not be used, and the Investigator or his designee will notify the sponsor or sponsor's designee for replacement of the study drug, and for direction on the return of the unused vial.
- Heart rate and blood pressure will be assessed pre-, immediately post, and 30 minutes post administration. Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.
- The participant will be monitored for at least 30 minutes for serious acute reactions as hypersensitivity or bioactive (labile) iron reactions to non-dextran IV iron products have rarely been reported. The reactions include: hypotension, loss of consciousness, bronchospasm with dyspnea, shortness of breath, and seizures.
    - In the event a serious acute reaction is seen, the site must have the capability to provide appropriate resuscitation measures. These may include IV NS, IV epinephrine, steroids, and/or antihistamines.

5.4 Drug Accountability

Investigators will keep records of the receipt, administration and return of the study drug (FCM). They will not allow the study drug to be used for purposes other than as directed by this protocol. The investigator agrees that he/she will not supply study medication to any persons other than those randomized in the study, or to investigators not listed on the FDA 1572. When the study is completed, or if it is prematurely terminated, a final inventory of all clinical supplies must be compiled and the remainder of the unused study drug will be returned to Luitpold Pharmaceuticals, Inc., or destroyed on site, per the site's documented locally accepted policies. All data regarding the study drug must be recorded as per the Monitoring Plan.

5.5 Concomitant Medication

All Concomitant medications will be recorded in the eCase Report Form (eCRF).

No prophylactic medications specifically for administration of study drug may be administered prior to study drug administration without prior approval from Luitpold Pharmaceuticals, Inc. Other standard therapies are permitted.

5.6 Blinding

All participants and blinded study staff will be blinded to the content of study drug for the duration of the trial.

During the period of study drug administration, the blinded personnel will not be with the subject or in a location that could result in the blind being inadvertently broken. However, the Principal Investigator or designee will be available in the event of an emergency, and/or the need for adverse event assessment. All blinded study personnel will be blinded to the post-treatment iron indices and serum phosphorous laboratory results, as the values may break the blind.

The blinding will be maintained until the study is complete, and the database has been locked. In the event of an emergency that would require the investigator to be aware of the treatment allocation prior to database lock, the investigator can obtain this information, on a per participant basis. **It is recommended to contact the sponsor's Medical Monitor or designee prior to unblinding.** If a participant's treatment assignment is unblinded, the sponsor must be contacted immediately via telephone.

6.0 STUDY PROCEDURES

6.1 Informed Consent

Prior to any study specific procedures, the investigator or his or her designee must explain to each participant the nature of the study, its purpose, procedures to be performed, expected duration, and the benefits and risks of study participation. After this explanation the participant must voluntarily sign an informed consent statement (Required Elements of Informed Consent, 21 CFR 50.25). The participant will be given a copy of the signed consent form.

6.2 Screening Phase (Day -28 to Day 0)

6.2.1 Screening Visit

Each participant who has signed the informed consent and qualifies for inclusion will undergo the following clinical evaluations to confirm eligibility for the study (all procedures to be performed by blinded study personnel):

- Demographic and medical history including NYHA heart failure class and prior heart failure hospitalizations
- Left ventricular ejection fraction (historical values may be used if performed within 12 months of the screening visit, or 24 months if LVEF ≤25%) must be performed at least 12 weeks after major cardiac intervention-including CABG, valvular intervention, or cardiac resynchronization therapy device implantation
- Blood samples for hematology, iron indices, and NT-proBNP (local laboratory)
- Concomitant medications
- Review inclusion/exclusion criteria
- Enter participant in the Interactive Response Technology (IRT) system to obtain screening number.

Participants who do not meet study entry criteria should be entered into the IRT system as a screen failure. If all entry criteria can be verified qualified participants may be randomized and proceed to the Day 0 visit on the same day as the screening visit.

6.3 Treatment Phase (Day 0 to Day 7)

6.3.1 Day 0 Visit

All eligible participants will be randomized to either Group A or Group B in a 1:1 ratio based on a pre-determined randomization schedule via an IRT system.

The following will be obtained and/or completed before contacting IRT for randomization:

For all participants (all procedures to be performed by blinded study personnel):

- Verify all inclusion and exclusion criteria
- Height and weight
- Targeted physical exam
- Blood samples for central lab hematology, chemistries and iron indices for all participants; Vitamin D, PTH for participants at sites selected for post dose chemistry follow-up visits.
- Review concomitant medications
- Urine pregnancy test (women of childbearing potential only)
- Administer 6MWT per standardized procedure

The IRT system will then be contacted by an **Unblinded** study team member and all eligible participants will be randomized to either Group A or Group B in a 1:1 ratio with stratification by region based on a pre-determined randomization schedule. After assignment of the treatment group the following will occur:

Group A:

- Verify amount of single FCM dose (15mg/kg up to a maximum dose of 750 mg) (unblinded staff)
- Pre-administration, obtain heart rate, blood pressure, and body temperature (blinded staff)
- Administer FCM as a slow IV injection at the rate of approximately 2 mL /minute taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff)
- Document start and stop time of FCM administration and the total dose and volume administered (unblinded staff)
- Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after FCM administration (blinded staff)
- Adverse event / serious adverse event assessment (starting at beginning of FCM injection) (blinded staff)

Group B:

- Pre-administration, obtain heart rate, blood pressure, and body temperature (blinded staff)
- Administer a 15 mL dose of placebo (normal saline) as a slow IV injection at the rate of approximately 2 mL /minute taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff).
- Document start and stop time of placebo administration and the total volume administered (unblinded staff).
- Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after placebo administration (blinded staff)
- Adverse event and serious adverse event assessment (starting at beginning of placebo injection) (blinded staff)

6.3.2 Day 7 Visit

All participants will return to the clinic for study drug dosing on Day 7($\pm$2). Prior to the administration of the study drug, the participant will be evaluated clinically to assess the development of clinically significant conditions that may contraindicate dosing.

Group A participants the following will be performed:

- Verify amount of single FCM dose (15mg/kg up to a maximum dose of 750 mg) (unblinded staff)
- Pre-administration, obtain heart rate, blood pressure, and body temperature (blinded staff)
- Administer FCM as a slow IV injection at the rate of approximately 2 mL /minute taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff).
- Document start and stop time of FCM administration and the total dose and volume administered (unblinded staff)
- Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after FCM administration (blinded staff)
- Adverse event / serious adverse event assessment, including evaluation of potential endpoint events (see section 10.2; blinded staff)
- Review concomitant medications

Group B participants the following will be performed:

- Pre-administration, obtain heart rate, blood pressure, and body temperature (blinded staff)
- Administer a 15 mL dose of placebo (normal saline) as a slow IV injection at the rate of approximately 2 mL /minute taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff).
- Document start and stop time of placebo administration and the total volume administered (unblinded staff)
- Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after placebo administration (blinded staff)
- Adverse event/serious adverse event assessment, including evaluation of potential

endpoint events (see section 10.2; blinded staff)Review concomitant medications (blinded staff)

6.4 Follow-Up Phase

6.4.1 Chemistry Laboratory Collection Subset -Day 21 (± 7)

In a subset of sites approximately 500 participants, will have central lab clinical laboratories (chemistry, hematology and iron indices) collected following the initial and each subsequent course (approximately every 6 months) of study drug treatment (FCM or Placebo). The participants will have chemistry laboratories collected 21±7 days post the first treatment for that course (i.e. Study Days 21±7, 201±7, 381±7, 561±7, 741±7, 921±7…EOS). (blinded staff)

6.4.2 90 Day Follow-Up

Following the initial and all subsequent courses of study drug treatments each participant will be contacted in person or via telephone 90±14 days post the first treatment for that course (i.e. study Days 90±14, 270±14, 450±14, 630±14, 810±14, 990±14…EOS)

During these visits the following will be performed:

- Adverse event / serious adverse event assessment, including evaluation of potential endpoint events (see **section 10.2**). (blinded staff)

6.4.3 6 Month Laboratory Evaluation

Participants will receive an additional course of study medication every 180 (±7) days. Within 2 to 20 days prior to these scheduled dosing visits, all participants will return to the clinic to obtain central lab hematology, chemistry, and iron indices laboratory tests. (Blood to be collected by blinded staff)

6.4.4 Additional Study Drug Dosing (Every 6 Months)

All participants will be dosed every 6 months. At each 6-month interval, a course of 2 doses of study drug will be administered as described above for Day 0 and Day 7 (Section 6.3). For group A, FCM will be administered if Hgb < 13.5 g/dL (females) or <15.0 g/dL (males) and serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%; placebo (normal saline) will be administered to participants in the FCM group who do not meet the above criteria. All group B participants will receive placebo (normal saline)

6.4.4.1 6 Month Dosing Visit #1 (Days 180±7, 360±7, 540±7, 660±7, 840±7, 1,020±7…EOS)

On the first of the 2 dosing visits, the following will be performed by blinded study staff for all participants:

- Weight
- Urine pregnancy test (women of childbearing potential only)
- Adverse event / serious adverse event assessment, including evaluation of potential endpoint events (see section 10.2).
- Review concomitant medications
- Administer 6MWT per standardized procedure (at the 6 and 12 month visits).

For Group A participants the following will be performed:

- Verify if participant will receive FCM or placebo, based on the following criteria from recent labs (within 20 days). Participants will receive FCM if the Hgb <13.5 g/dL (females) or <15.0 g/dL (males) and serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%. If the participant does not meet these criteria, placebo (normal saline) will be administered. (unblinded staff)
- As appropriate based on criteria above, verify amount of single FCM dose (15mg/kg up to a maximum dose of 750 mg) or placebo (15 mL). (unblinded staff)
- Pre-administration, obtain heart rate, blood pressure, and body temperature. (blinded staff)
- Administer FCM or placebo as a slow IV injection at the rate of approximately 2 mL /minute. Appropriate measures must be taken to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff)
- Document start and stop time of IV administration, and the total dose and volume administered (unblinded staff)
- Post-administration of FCM, obtain heart rate and blood pressure immediately after and 30 minutes after FCM administration (blinded staff)

For Group B participants the following will be performed:

- Pre-administration, obtain heart rate, blood pressure and body temperature. (blinded staff)
- Administer a 15 mL dose of placebo (normal saline) as a slow IV injection, at the rate of approximately 2 mL /minute. Taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff)
- Document start and stop time of placebo administration and the total volume administered. (unblinded staff)
- Post-administration of placebo, obtain heart rate and blood pressure immediately after and 30 minutes after placebo administration(blinded staff)

6.4.4.2 Six Month Dosing Visit #2 (Days 187±7, 367±7, 547±7, 667±7, 847±7, 1,027±7…EOS)

The second of the 2 dosing visits should occur at Day 7 (±2) after the first, with the following performed for all participants:

- Adverse event / serious adverse event assessment, including evaluation of potential endpoint events (see **section 10.2**) (blinded staff), and review of concomitant medications (blinded staff).

For Group A participants the following will be performed:

- Verify amount of single FCM dose (15mg/kg up to a maximum dose of 750 mg) or placebo (15 mL). Note: participant should receive the same product (FCM or placebo) as received at the first dose of this course of treatment. (unblinded staff)
- Pre-administration, obtain heart rate, blood pressure, and body temperature. (blinded staff)
- Administer FCM or placebo as a slow IV injection at the rate of approximately 2 mL /minute. Taking appropriate measures to ensure the participant and all blinded staff

members remain blinded to the treatment being administered (unblinded staff).
- Document start and stop time of IV administration and the total dose and volume administered. (unblinded staff)
- Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after FCM administration. (blinded staff)

For Group B participants the following will be performed:

- Pre-administration, obtain heart rate, blood pressure, and body temperature. (blinded staff).
- Administer a 15 mL dose of placebo (normal saline) as a slow IV injection at the rate of approximately 2 mL /minute. Taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff)
- Document start and stop time of placebo administration and the total volume administered. (unblinded staff)
- Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after placebo administration. (blinded staff).

6.5 End of Study Visit

End of study visits for all participants will be scheduled once the last participant has reached 12 months on study and at least 771 participants have experienced an event of cardiovascular death or hospitalization for heart failure. When possible, the participants should return to the clinic and the following will be performed by blinded study staff:

- Targeted physical exam
- Vital signs including BP and heart rate
- Blood samples for central lab hematology, chemistries, iron indices and NT-proBNP.
- Urine pregnancy test (women of childbearing potential only)
- Review of concomitant medications
- Adverse event / serious adverse event assessment, including evaluation of potential endpoint events (see **section 10.2**).

6.6 Laboratory Assessments

Serum samples for laboratory analyses must be obtained at all appropriate visits. Screening laboratory values will be analyzed locally. All other visit laboratory samples will be analyzed by a central clinical laboratory. All laboratory testing will be provided to the investigator or his/her medically qualified designee for review and assessment. Post dose iron indices and serum phosphorus results will be provided to the designated unblinded investigator for assessment. The laboratory assessments will be determined as listed in **Section 3.3**:

Hematology:	Hgb, Hct, RBC, WBC, MCV, MCH, MCHC, RDW, platelets, differential count, and reticulocyte count
Chemistry:	Sodium, potassium, chloride, BUN, creatinine, albumin, alkaline phosphatase, total bilirubin, GGT, AST, ALT, LDH, calcium, phosphorus, glucose, bicarbonate, and magnesium

Iron indices:	Serum iron, serum ferritin, total iron binding capacity (TIBC), and percentage serum transferrin saturation (TSAT)
Other:	Vitamin D, Parathyroid Hormone, NT-proBNP

7.0 ASSESSMENT OF SAFETY

7.1 Adverse Events

Any untoward medical event experienced by a participant during the course of this clinical trial, whether or not it is related to the investigational product, at any dose, is considered an adverse event (AE).

For any laboratory abnormality, the investigator, or his/her medically qualified designee, will make a judgment as to its clinical significance. If the laboratory value is outside the normal limits and is felt to represent a clinically significant worsening from the baseline value, it should be considered an adverse event. If the laboratory value is outside the normal range, but not an adverse event, the investigator should comment on the findings (i.e. “not clinically significant” or “unchanged from baseline”) in the source documentation [laboratory report].

The investigator should use **Table 7.1.1** to assign the adverse event severity grade.

Table 7.1.1 Grading of Adverse Event Severity

Grade	Adjective	Description
1	Mild	Does not interfere with the participant's usual function
2	Moderate	Interferes to some extent with participant's usual function
3	Severe	Interferes significantly with participant's usual function
4	Life-threatening	Results in a threat to life or in an incapacitating disability
5	Death	Results in Death

Timing: Adverse events and serious adverse events will be reported, as described below in Section 7.2, from the time of randomization through the end of study. Adverse events for participants randomized and who terminate early will be reported for 30 days after the last treatment.

Relationship (Causality): The Investigator will be asked to document his/her opinion of the relationship of the event to the study drug* as follows:

- NONE There is *no* evidence of any causal relationship.
- UNLIKELY There is *little* evidence to suggest there is a causal relationship. There is *another reasonable explanation* for the event (e.g., the participant's clinical condition, other concomitant treatments).
- POSSIBLE There is *some* evidence to suggest a causal relationship (i.e. there is a reasonable possibility that the adverse experience may have been caused by the agent). However, the influence of *other factors may have contributed* to the event (e.g., the participant's clinical condition, other concomitant events).
- PROBABLE There *is evidence* to suggest a causal relationship, and the influence of other factors is *unlikely*.

* For the purposes of this trial, "study drug" is defined as:

FCM

OR

Placebo

7.2 Reporting of Adverse Events

For the purposes of this study, any AE that does not meet the protocol definition of a serious AE is considered non-serious. Non-serious AEs will not be collected for this trial, except for AEs leading to cessation of study medication. Disease progression can be considered as a worsening of a patient's clinical condition attributable to the disease in the patient population for which the

study medication is being studied. It may be an increase in the severity of the disease under study, and/or increases in the symptoms of the disease. The development of the following cardiovascular disease events will be recorded in the eCRF, however they should be considered as disease progression and will not be reported as an AE/SAE during the study unless determined to be clinical endpoints. These include the events listed in **Section 7.4**, "Reporting of Events that May Require Adjudication." Adverse experiences will be elicited by nonspecific questions such as "Have you noticed any problems?" Participants will be encouraged to report adverse events at their onset.

7.3 Serious Adverse Events

Definition: An adverse event is classified as SERIOUS if it meets any one of the following criteria:

- **Death**
- **Life-Threatening:** The participant was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the participant's death.
- **Hospitalization (initial or prolonged):** Required admission to the hospital or prolongation of a hospital stay except events which are components of the primary or secondary endpoints which will be adjudicated by the CEC Committee as noted above.
- **Disability:** Resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the participant's body function/structure, physical activities or quality of life.
- **Congenital Anomaly/Birth Defect.**
- **Important medical events:** Other medically important events that, in the opinion of the investigator, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above.

Suspected clinical endpoint events that may traditionally meet the definition of an SAE, will not be reported by the sites in this trial as an SAE. Those events will therefore not to be reported to the sponsor's Drug Safety Surveillance department.

Certain events of interest that are related to heart failure (serious and non-serious) and selected expected (described in the label) serious side effects of the study drug will be listed on the eCRF and not be reported by the site as an SAE.

These events will be monitored by the Data Safety Monitoring Board to ensure participant safety.

Additionally suspected clinical events that are reviewed by the CEC but do not meet the criteria of an endpoint event will be reviewed by the safety surveillance team for possible unreported SAEs.

Reporting: **Any SAE as defined by this protocol, starting with the time of randomization, that is to be reported (as outlined in the section above) must be reported immediately (by the end of the next business day) to Luitpold Pharmaceuticals, Inc. This occurs through entry into the eCRF by the local investigator/coordinator and completing the SAE module. In the**

event that the eCRF module is not available the investigator will contact the Study Safety Monitor at

Luitpold Pharmaceuticals, Inc.

[redacted]

[redacted]

The local investigator is responsible for reporting SAEs to their local IRB/ Ethics Committee based on local reporting guidelines (which may be different than those specified in this protocol). The responsible investigator should institute appropriate diagnostic and therapeutic measures and keep the participant under observation for as long as is medically indicated.

7.4 Reporting of Suspected Study Endpoint Events that May Require Adjudication

The following events, which are the components of the primary or secondary endpoints will be adjudicated by the Clinical Events Classification (CEC) Committee of the Duke Clinical Research Institute (DCRI) for both FCM and Placebo and will not require reporting to the sponsor as an SAE:

- Cardiovascular Death including:
  - Death due to Heart Failure
  - Death due to Acute Myocardial Infarction
  - Sudden Cardiac Death
  - Death due to Stroke
  - Death due to other cardiovascular causes
- Hospitalization for heart failure
- Non-Cardiovascular death
- Hospitalization for myocardial infarction
- Hospitalization for stroke
- Other Cardiovascular hospitalizations
- Urgent heart failure visits

Therefore, any event that may possibly constitute one of these endpoints will be evaluated by the CEC Committee by a procedure to be described in separate documentation. A description of the CEC Committee and the definitions of the above clinical endpoints may be found in Section 10.2.

8.0 STATISTIC

All statistical tests will be two-tailed. Type I error of 0.05 is assumed unless otherwise specified. No adjustments for multiple testing will be made.

8.1 Stratification/Randomization

Participants who meet the inclusion/exclusion criteria will be randomized in a 1:1 ratio on Day 0 to FCM or Placebo with stratification by region.

8.2 Analysis Populations

The Intent-To-Treat (ITT) Population will consist of all participants randomized to a treatment group in the study regardless of compliance with the study medication. For all analyzed using the ITT population, participants will be analyzed as randomized. This is the primary population of all efficacy analyses.

The Per-Protocol Population is a subset of the ITT population excluding participants who complied with the randomized treatment for less than 50% of the follow-up. In cases of medication error, treatment assignments in the per-protocol analysis will be analyzed according to the actual treatment received.

8.3 Disposition and Baseline Characteristics

The number and percent of participants who are randomized, treated with randomized therapy, prematurely discontinue, and complete the study will be summarized. The number and percent of participants will be summarized for each reason for premature discontinuation.

Categorical baseline characteristics (e.g., sex and race) will be summarized with the number and percent of participants in each treatment group with the characteristic. Quantitative characteristics (e.g., age and weight) will be summarized with the mean, median, standard deviation, minimum value, and maximum value. Baseline characteristics will be summarized for the safety and ITT populations.

8.4 Endpoints and Definitions

8.4.1 Primary Outcome

The primary outcome follows an ordinal scale of clinical severity comprised of 1) death, 2) number of hospitalizations for heart failure (as defined in **section 10.2**) evaluated at one year; or 3) change in 6MWT evaluated at 6 months.

8.5 Secondary Outcomes

The following secondary outcomes will be evaluated in the hierarchy listed below.

1. Time to first event of the composite of cardiovascular death or heart failure hospitalization. The composite endpoint will be composed of adjudicated occurrence (as defined in section 10.2) of one of the following:

    a. Cardiovascular Death
        i. Death due to Heart Failure
        ii. Death due to Acute Myocardial Infarction
        iii. Sudden Cardiac Death
        iv. Death due to Stroke
        v. Death due to other Cardiovascular Causes
    b. Hospitalization for Worsening Heart Failure

2. Mean change in 6MWT from baseline to 12 months

3. Time to first event of the composite of cardiovascular death or intervention for worsening heart failure (hospitalization or urgent heart failure visits)
4. Time to first event of the composite of cardiovascular death and cardiovascular hospitalizations
5. Time to cardiovascular death

Additional events to be adjudicated for analysis of the secondary endpoints include:

a) Non-cardiovascular death
b) Hospitalization for myocardial infarction
c) Hospitalization for stroke
d) Other cardiovascular hospitalizations
e) Urgent heart failure visits

An endpoint adjudication committee at DCRI will review all potential events comprising all endpoints, and make the final determination whether an endpoint event has occurred for each participant (See Section 10.2).

8.6 Primary Comparison

Each participant from the treatment arm gets ranked/compared with each participant from the control arm based on the 12-month experience for Death and Hospitalizations for heart failure and 6 month results for change in 6MWT to determine treatment response per the following hierarchy:

1. **Death**
   If both die, the one who survives longer is better off;
   If one dies and one does not, the one that survives is better off;
   If neither dies, examine hospitalizations for heart failure.

2. **Hospitalizations for heart failure**
   The one with fewer hospitalizations is better off;

   If neither has been hospitalized for heart failure or the number heart failure hospitalizations is equal, compare change in 6MWT.

3. **Change in 6MWT**
   The one with higher change in 6MWT is better off;

Statistical Test

The main comparison will be conducted using the Wilcoxon-Mann-Whitney test. The null hypothesis being tested is that a randomly chosen participant in the treatment arm is equally likely to be ranked better or worse than a randomly chosen participant in the control group. The two-sided alternative is that the participant is not equally likely to be ranked better or worse. In addition to performing the test we will estimate the probability that a participant in the treatment arm has a better rank than a participant in the control arm and its corresponding confidence interval.

The above comparison of participants in the treatment versus control arms is equivalent to ranking all participants according to their experience. At one end of the ranking are participants with the best experience - those alive and not hospitalized for worsening heart failure ordered according to their improvement in 6MWT; at the opposite end are those who die ordered according to their survival time. Those participants alive but hospitalized are in the middle, ordered according to their number of hospitalizations for worsening heart failure and then by their change in 6MWT. The non-parametric Wilcoxon-Mann-Whitney test sums the ranks of those in the treatment arm and compares them with the sum of ranks in the control arm.

In all analyses the number of hospitalizations (and the number of days in the hospital in the sensitivity analysis described below) will be adjusted for the time on follow-up. This adjustment applies only to individuals who are alive at the end of follow-up (the comparison in those who die will be resolved based on time to death) and will be accomplished by dividing the observed number by time at risk in years. For individuals who complete the pre-specified 12 months of follow-up, time at risk equals 1. For all others, it is equal to the fraction of 12 months that the person remained in the study.

8.7 Secondary Comparisons

8.7.1 Top Secondary Comparison: Time to first event of cardiovascular death or hospitalization of heart failure

This analysis will compare time to first occurrence of cardiovascular death or hospitalization for heart failure. The Cox proportional hazards model will be employed to conduct this comparison. The test will be two-tailed and will be performed at an overall α of 0.05. This analysis will be performed by the ITT principle based on randomized treatment assignment and we expect adequate power to detect a pre-specified relative risk reduction of 20%.

Sensitivity Analysis

In a sensitivity analysis we will add another layer to the hierarchy described above – in individuals who have been hospitalized for heart failure during follow-up, ties in the numbers of hospitalizations will be resolved based on the total number of days in the hospital during follow-up, before proceeding to comparison of differences in the 6MWT.

8.7.2 Change in 6 Minute Walk Test

Mean change in 6MWT distance from baseline to 12 months will be compared using linear regression adjusting for baseline value of 6MWT.

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8.7.3 Secondary Outcomes based on time to first event

The time to each of the remaining secondary outcomes (Incidence of cardiovascular deaths and cardiovascular hospitalizations, Incidence of cardiovascular death or intervention for worsening heart failure (hospitalization or urgent heart failure visits) and Incidence of cardiovascular deaths) will be compared using the Cox proportional hazards model.

8.8 Sample Size and Statistical Power

The study design allows for sufficient power for both the primary and top secondary outcomes.

Numerical simulations based on multivariate normal vectors were conducted to estimate power for the primary treatment comparison based on the following assumptions about events rates described in **Table 8.8.1**.

Table 8.8.1. Assumptions About Event Rates for Primary Outcome

Ranked tier at 12-month endpoint (6 month for 6 MWT)	Control	Treatment
Death total	8%	6.8%
Death without hospitalization	4%	3.4%
Death with hospitalization	4%	3.4%
Hospitalizations in survivors		
1	6%	4.8%
2	3%	2.4%
3 or more	1%	0.8%
Change in 6 Minute Walk Test	Mean = 0 SD = 90	Mean = 18 SD = 90

With 3014 patients (1507 per arm) and 2.5% annual loss to follow-up for clinical outcomes and 15% of individuals with missing 6MWT at 6 months (unable to perform or lost to follow-up), projected simulations estimate 90% power at an overall two-sided significance level of 0.01, accounting for one interim analysis as described in section 8.10.

For the top secondary composite, an assumed event rate of 0.0128 per month in the control arm which represents conservative 75% discounting of the event rate obtained by the FCM meta-analysis [**Anker 2015**]. The anticipated hazard ratio was set at 0.80 (20% reduction). Uniform enrollment is assumed over the period of 30 months, with an anticipated minimum follow-up of 12 months (required minimum of 6 months), anticipated maximum follow-up of 42 months (no required maximum), and monthly loss to follow-up of 0.0021 (2.5% annualized). With these assumptions, 1500 per study arm (3000 total) provides 90% power to reject the null hypothesis of no difference between treatment arms when tested at an overall two-sided level of significance α=0.05, accounting for one interim analysis as described in section 8.10. This results in a total of 771 events necessary to achieve the desired power. Thus, the trial has the potential opportunity to be stopped at a point where the projected number of events reaches 771, but no earlier than the last participant reaching 12 months of follow-up.

The primary and top secondary outcome will be tested sequentially, and thus, no multiplicity adjustment is necessary.

8.9 Handling of Missing Data

Every effort will be made to limit the number of missing data points. The trial will be conducted in jurisdiction which will allow ascertainment of vital status even in individuals who discontinue the study. Participants who discontinue taking study drug should be encouraged to continue participation in the trial so that endpoint data can be collected. Furthermore, consent will be obtained to examine hospital records where feasible. Partnership with transportation companies

will be fostered to decrease the burden of travel to clinic visit and increase the likelihood of the final study visit taking place.

The prospective plan for the handling of missing data is as follows:

The primary analysis will rely on a multiple imputation model, with Markov chain Monte Carlo algorithm based on the totality of observed data. One exception to this rule will be individuals unable to perform the 6MWT test at 6 months will have their value imputed as the worst observed change in 6MWT.

Two supporting analyses will be undertaken. The first one will use multiple imputation for clinical outcomes, but will impute the worst observed change in 6MWT to all individuals who do not have this measurement, regardless of the reason.

The second series of analyses will perform tipping point assessments to determine the sensitivity of the observed result to the missing data. Given the multi-dimensional nature of outcomes, tipping point analyses will be performed separately for each outcome: mortality, hospitalization for heart failure and 6MWT.

8.10 Stopping Rules and Interim Analysis

A Data and Safety Monitoring Committee (DSMB), with statistical support from DCRI will review safety data, including a tally of the composite outcome events at least every 6 months (See Section 10.3). The DSMB can recommend stopping the study for safety concern at any point. In addition, one interim analysis is planned to determine if an early stopping for an overwhelming efficacy should be recommended or if an increase in sample size is warranted. This analysis will be conducted after 2250 (75%) participants have been enrolled. Significance level will be set at 0.0001 for this analysis, resulting in an adjusted significance level for the final analysis of 0.0099 for the primary endpoint and 0.0499 for the first secondary endpoint, preserving the overall significance at 0.01 and 0.05, respectively. Conditional power will be estimated based on data accrued to date and presented to the DSMB. The DSMB may recommend that the study continues as planned, is stopped for overwhelming efficacy or that the sample size or trial duration is increased to achieve at least 80% conditional power but not by more than 50% of the original sample size or duration.

9.0 ADMINISTRATIVE CONSIDERATIONS

9.1 Retention and Availability of Records

Investigators are required to maintain all study documentation, including a copy of the CRFs, Informed Consent documents, and adequate records for the receipt and disposition of study medications, for a period of two years following a supplemental application for the drug for the indication being investigated, or until two years after the drug investigational program is discontinued.

The Investigator must make study data accessible to the monitor, Sponsors, or other authorized representatives of the Sponsor and Regulatory Agency (i.e., FDA inspectors.) A case history for each participant must be maintained, that includes the signed Informed Consent form and copies of all study documentation related to that participant. The investigator must ensure the availability

of source documents including the electronic health record, if applicable, from which the information on the eCRF was derived.

9.2 Investigator Responsibilities

By signing the Form FDA 1572 the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor, except when necessary to protect the safety, rights or welfare of participants.
2. Personally conduct or supervise the study (or investigation).
3. Inform any participants that the drug is being used for investigational purposes.
4. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet Federal guidelines, as stated in 21 CFR, parts 50 and 56.
5. Report to the Sponsor any adverse events that occur in the course of the study, in accordance with 21 CFR 312.64.
6. Have read and understood the Investigator's Brochure, including potential risks and side effects of the drug.
7. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
8. Maintain adequate and accurate records, in accordance with 21 CFR 312.62 and to make those records available for inspection with the Sponsor, their designated representative, the FDA or any agency authorized by law.
9. Ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for initial and continuing review and approval of the clinical study.
10. Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to participants or others (including amendments and IND safety reports).
11. Not make any changes in the research study without approval, except when necessary to eliminate hazards to the participant/participants.
12. To comply with all other requirements regarding the obligations of the clinical investigators and all other pertinent requirements listed in 21 CFR Part 312.

9.3 Financial Disclosure

All principal investigators and co-investigators will be required to complete FDA-required financial forms provided by Luitpold Pharmaceuticals, Inc. All signed financial disclosure forms must be submitted to the Sponsor prior to the site enrolling participants into the study.

9.4 Advertisement for Participant Recruitment

All advertisement for participant recruitment must be reviewed and approved by the Sponsor and the site's IRB prior to implementation. Advertisement may include but is not limited to: newspaper, fliers, radio, and television. Any compensation to the participant included in the advertisement must be identical to the compensation stated in the IRB-approved informed consent.

9.5 Documents Required for Study Initiation

Prior to study initiation, the investigator must provide Luitpold Pharmaceuticals Inc. or its designee with the following documentation:

- Curriculum Vitae and medical license for Principal Investigators and co-investigators.
- Form FDA 1572
- Financial disclosure form
- IRB approval of protocol and informed consent
- Copy of IRB approved informed consent
- IRB membership list or assurance number
- Protocol signature page
- IRB approval of any advertising for participant recruitment [if applicable]
- Copy of advertising [if applicable]
- IRB approval of translation of informed consent [if applicable]

9.6 Quality Control and Quality Assurance

9.6.1 Investigator Selection Criteria

Each investigator participating in this study will meet the following criteria:

- Accessible, interested, and available support staff.
- Availability of adequate facilities to support study requirements.
- Availability of physician emergency response at all times.
- Adequate time to conduct study.
- Adequate training and experience of personnel to conduct study.
- Ability to recruit enough participants to conduct study.

Prior to investigator selection, each site will be evaluated to ensure they meet the criteria noted above.

Luitpold Pharmaceuticals, Inc. and/or their designee will insure that no investigator is on FDA's Debarment List or Disqualified Investigator List.

9.6.2 Clinical Monitoring

This study will be monitored by the Sponsor (or its designee) in accordance with FDA and International Conference on Harmonisation Good Clinical Practices (GCPs), 21CFR Part 312. As part of a concerted effort to follow the study in a detailed and orderly manner, in accordance with established principles of GCP and applicable regulations, a Monitor will visit the site according to the monitoring plan and will maintain telephone and written communication throughout the duration of the study.

Periodic monitoring visits will be made to the site during the clinical study to assure that the Investigator obligations are fulfilled, and all applicable regulations and guidelines established by the protocol are being followed.

These visits will assure that the facility is still acceptable, the protocol and investigational plan are being followed, the IRB/EC has been notified of approved protocol changes as required, complete

study records are being maintained, appropriate and timely reports have been made to the sponsor or its representative and the IRB/EC, study drug inventory is controlled, and the Investigator is carrying out all agreed-upon activities.

In accordance with the FDA *Guidance for Industry: Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring,* a combination of on-site and centralized monitoring practices will be implemented in order to ensure participant protection, as well as quality and integrity of the clinical trial data while promoting efficiency. While the majority of monitoring will be conducted centrally, on-site monitoring will be performed based on the findings of previous on-site monitoring visits and centralized monitoring. During on-site monitoring, a percentage of the data will be compared among the eCRF (i.e. source document review, source document verification) and each participant's source documentation, and data discrepancies will be queried. See the trial specific risk based monitoring plan for additional details.

9.6.3 Quality Assurance Audit

For the purpose of data validation, the principal investigators will permit a member of the quality assurance unit of Luitpold Pharmaceuticals, Inc. or its designee to inspect the source data and compare them with the eCRFs. Pre-study audits, interim audits and post-study audits may be performed and may also include review of facilities, equipment, pertinent site documentation, and personnel qualifications. Notification of these audits will be sent to investigators in advance.

9.7 Ethics

9.7.1 Ethical and Legal Issues

This study will be performed in accordance with the U.S. Code of Federal Regulations on Protection of Human Participants (21 CFR 50), IRB regulations (21 CFR 56), the most recent revision of the Declaration of Helsinki, all applicable local and state regulations, 21 CFR Part 312, and applicable ICH guidelines.

9.7.2 Institutional Review Board

The Protocol and the Informed Consent must be approved by an appropriate Institutional Review Board (IRB) before the study is initiated. Documentation of this approval must be provided to the Sponsor or designee. The IRB must comply with current U.S. Regulations (21 CFR 56) for the protection of Human Subjects in Research. Investigators are responsible for the following:

- Obtain IRB approval of the protocol, Informed Consent, and any advertisements to recruit participants; obtain IRB approval for any protocol amendments and Informed Consent revisions before implementing the changes.
- Provide the IRB with any information it requests before or during the study.
- Submit progress reports and a final report to the IRB, as required, during the conduct of the study; request re-review and approval of the study as needed; provide copies of all IRB re-approvals and relevant communication with the Sponsor.
- Notify the IRB of all serious adverse events that occur or are reported to you by the Sponsor as required by the IRB.

9.7.3 Informed Consent

Each investigational site must provide the Sponsor (or designee) with a copy of the Informed Consent approved by the site's IRB. The Clinical Monitor will assure that each Informed Consent meets the requirements of Parts 50.20 and 50.25 of Title 21 of the CFR, which outlines the basic elements of informed consent and ICH guidelines prior to its use.

Informed consent must be obtained from each participant prior to enrollment. The informed consent will be provided to the participant in their native language. The Informed Consent must be signed and dated by each participant before entering the study, and prior to the performance of any study-specific procedures. The original signed consent form will be retained in the participant's study records, and a copy will be provided to the participant. Translations of the informed consent must be certified by a qualified translator and their use must be documented.

The Informed Consent documents the information the Investigator provides to the participant and the participant's agreement to participate. The Investigator will fully explain the nature of the study, along with the purpose, methods, anticipated benefits, potential hazards, and discomfort that participation might entail.

9.7.4 Good Clinical Practice

The conduct of the study will conform with the recommendations for clinical studies in humans as set out in the most current revision of the “Declaration of Helsinki”, the local legal requirements and the guidelines on “Good Clinical Practice”, [21 CFR Part 312 and ICH guidelines].

9.8 Data Handling and Record Keeping

9.8.1 Case Report Form

The eCRFs will be completed for each participant on this study. The participants in this study will be identified only by a participant number on these forms.

The eCRF used will be 21 CFR 11 compliant. The system used for data collection (eCRF) will meet all applicable regulatory requirements for recordkeeping and record retention as would be provided with a paper system. Security measures will be utilized to prevent unauthorized access to the data and to the computerized system. Changes made to data that are stored on electronic media will always require an audit trail, in accordance with 21 CFR 11.10(e).

The eCRFs must be reviewed and verified for accuracy by the Principal Investigator. An electronic copy of the eCRF will remain at the site at the completion of the study.

9.8.2 Confidentiality

All unpublished information given to the investigator or institution dealing with this study, study drug or the conduct, financial agreements, or methodologies used in this protocol, as well as information obtained during the course of the study, remains confidential and proprietary to the Sponsor [“Proprietary Information”]. The Investigator shall not disclose any such Proprietary Information to any third party without prior written consent from the sponsor [See also **Section 9.9** Publication Policy]. For purposes of this Section, “Investigator” includes, but is not limited to the Principal Investigator and/or his/her agents, designees, sub-investigators or other individuals

involved in the running, administration, collection or evaluation of participants or data for this study.

All pharmaceutical formulations supplied for the purpose of the trial shall remain the sole property of Luitpold Pharmaceuticals, Inc. They will be used for the purposes specified in the protocol. Any unused medication will be returned to the sponsor at the conclusion of the study.

No patent application based on the results of this study should be made by the investigator and all such rights assigned to Luitpold Pharmaceuticals, Inc., and no assistance should be given to any third party to make such an application without the written authorization of Luitpold Pharmaceuticals, Inc.

9.8.3 Termination of the Study

The study may be terminated if the DSMB, Sponsor, or Steering Committee discovers conditions arising during the course of the study, which indicate that the clinical investigation should be halted. The study may be terminated after appropriate consultation and discussion.

Conditions that may warrant study termination include, but are not limited to, the discovery of a significant, unexpected and unacceptable risk to the participants, failure of the investigator to enroll participants at an acceptable rate, insufficient adherence to the protocol requirements, completion of study objectives, or at the discretion of the sponsor.

9.8.4 Protocol Revisions

Changes in any portion of this protocol that affect participant safety or welfare or which alter the scientific validity of the study must be documented in the form of an amendment. This change must be signed by the appropriate Luitpold personnel and the investigator and be approved by the site's IRB, before the revision may be implemented. The protocol revision will be submitted to the FDA.

9.8.5 Protocol Administrative Changes

Clarification or interpretation of the study protocol or changes in the methods of statistical analysis may be documented in the form of a numbered memo or other applicable document (charter, plan, etc.). Numbered memos do not typically require the investigator’s signature or IRB approval.

9.9 Publication Policy

All information resulting from this study is the Proprietary Information of Luitpold Pharmaceuticals, Inc., as per the Confidentiality Section of this protocol. The Steering Committee will be responsible for the manuscript describing the main study results, and oversee publications requiring trial data. A separate publication charter will govern the process of publications.

Luitpold Pharmaceuticals, Inc., and the Steering Committee shall have final and sole control over the content of any publication. The Principal Investigator and any sub-investigators may make presentations on the study, or may publish results of the study at their site, but only after the results of the study have been published, or with the prior approval of Luitpold Pharmaceuticals, Inc.

The Investigator will provide to the Sponsor any announcement, publication, or presentation of data from this study for the Sponsor's review and comments at least 10 days in advance of such disclosure. Sponsor may, at its sole discretion, require the removal of any proprietary information from the disclosure. The Investigator agrees to provide the Sponsor, at the Sponsor's discretion, with any byline credit in any publication proposed by the Investigator. This is in order to enable Luitpold Pharmaceuticals, Inc., to make constructive comments about the manuscript or text and to give the opportunity of assessing whether patent protection should be sought by Luitpold on any results or ideas connected with the study.

10.0 GOVERNANCE COMMITTEES

10.1 Steering Committee (SC)

The SC will be responsible for oversight of the study. The SC chair will be Dr. Adrian Hernandez of DCRI. The SC will consist of 4-8 members including the chair, primarily from academic institutions, as well as representation of the Sponsor. The SC will consist of experts in heart failure as well as cardiovascular outcomes trials.

The key functions of the SC will be to:

1. Review and approve the main protocol, amendments, and the Statistical Analysis Plan.
2. Determine the time to terminate the study based on recommendations from the DSMB and other available information.
3. Review and approve any substudies.
4. Draft the manuscript describing the main study results and oversee all publications requiring trial data
5. Participate where appropriate in scientific meetings providing updates of study progress.
6. Oversee trial subcommittees including the Clinical Endpoint Committee and the Data Safety Monitoring Board
7. Assume the role of the publications committee and review, authorize and prioritize proposals for publications which require trial or substudy data samples and assign writing groups

10.2 Adjudication by the Clinical Endpoint Classification (CEC) Committee

A Clinical Event Committee (CEC) will be created for this trial to review and adjudicate each suspected endpoint event while blinded to treatment in this study. The CEC for this trial will consist of cardiologists, neurologists, and physicians with clinical expertise from DCRI or other academic institutions. The CEC Chair will lead the development of the definitions of endpoints, instructions for interpretation, and provide ongoing oversight to the CEC members for this trial to ensure that events are adjudicated in consistent fashion over time. The CEC members, as well as those overseeing the CEC, will not be investigators in the study, or be otherwise directly associated with the sponsor, and will remain blinded to treatment throughout the study and the adjudication process. The CEC and the adjudication process will be described in detail in a separate CEC charter.

Adjudicated Endpoints

10.2.1 Death

All deaths will be categorized as **Cardiovascular or non-Cardiovascular** based on the definitions below. In addition, all deaths will further be sub-typed based on the specific cardiovascular categories defined below. Non-cardiovascular deaths will not be further adjudicated.

The cause of death will be determined by the principal condition that caused the death, not the immediate mode of death. For example, if a participant is hospitalized and undergoing treatment for worsening heart failure dies of ventricular tachycardia, this would be classified as a heart failure death. CEC physicians will utilize all available information provided, along with clinical expertise in their adjudication of cause of death.

10.2.1.1 Death Due to Cardiovascular Death

Cardiovascular death includes death resulting from an acute MI, sudden cardiac death, death due to heart failure, death due to stroke, and death due to other CV causes.

10.2.1.2 Death Due to Heart Failure

Death due to heart failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure regardless of heart failure etiology. Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

Deaths that occur during a heart failure hospitalization will generally be attributed to heart failure, even if there is another immediate mode of death (e.g, ventricular fibrillation). Deaths that occur in hospice or other similar palliative care setting for heart failure will generally be attributed to heart failure.

10.2.1.3 Death Due to Acute Myocardial Infarction

Death due to acute MI refers to a death by any CV mechanism (e.g. arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) 30 days after a MI related to the immediate consequences of the MI, such as progressive heart failure or recalcitrant arrhythmia. We note that there may be assessable mechanisms of CV death during this time period, but for simplicity, if the CV death occurs≤30 days of the MI, it will be considered a death due to MI.

Acute MI should be verified to the extent possible by the diagnostic criteria outlined for CV hospitalization for acute MI, or by autopsy findings showing recent MI or recent coronary thrombosis.

Death resulting from a procedure to treat a MI, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from MI should also be considered death due to acute MI.

If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead ECG could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Death resulting from a procedure to treat a myocardial infarction (e.g. PCI, CABG), or to treat a complication resulting from MI, should also be considered death due to acute MI.

10.2.1.4 Sudden Cardiac Death

Sudden Cardiac Death refers to death that occurs unexpectedly and not following an acute MI, and includes the following deaths:

- Death witnessed and occurring without new or worsening symptoms.
- Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute myocardial infarction.
- Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator (ICD) review)
- Death after unsuccessful resuscitation from cardiac arrest. (e.g., ICD unresponsive sudden cardiac death, pulseless electrical activity arrest)
- Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology
- Unwitnessed death in a participant seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information about the participant's clinical status preceding death should be provided, if available)

General Considerations

- Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a participant is seen alive ≤24 hours (or a reasonable period when otherwise clinically stable) of being found dead OR circumstances suggest sudden death, sudden cardiac death should be recorded

Typical scenarios include:

- Participant well the previous day but found dead in bed the next day
- Participant found dead at home on the couch with the television on

For participants who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (e.g., participant found dead in bed, but who had not been seen by family for several days).

"Undetermined cause of death" will be considered as "CV death" for purpose of analysis.

10.2.1.5 Death Due to Stroke

Death due to Stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke in **Section 10.2.2.3** (Hospitalization for Stroke).

10.2.1.6 Death Due to Other Cardiovascular Causes

Death due to Other Cardiovascular Causes refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolus or peripheral arterial disease).

10.2.1.7 Non-Cardiovascular Death

Non-cardiovascular death is defined as any death that is not thought to be CV in nature. Deaths from Non-CV causes will not be further subclassified.

10.2.1.8 Undetermined Cause of Death

Death not attributable to one of the above categories of CV death, or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g. the only information is "participant died"), or when there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classified as CV or non-CV, and the use of this category of death, therefore, should be discouraged and should apply to few participants..

All deaths adjudicated as "undetermined cause" will be presumed cardiovascular deaths, and as such, are part of the cardiovascular mortality endpoint.

10.2.2 Cardiovascular Hospitalizations

The participant's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date, if admission and discharge times are unavailable).

10.2.2.1 Hospitalization for Heart Failure

A Heart Failure hospitalization is defined as an event that meets **ALL** of the following criteria:

1) The participant is admitted to the hospital with a primary diagnosis of heart failure
2) The participant's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date, if admission and discharge times are unavailable).
3) The participant exhibits documented new or worsening symptoms due to heart failure on presentation, including at least ONE of the following:
    a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
    b. Decreased exercise tolerance
    c. Fatigue
    d. Other symptoms of worsened end-organ perfusion or volume overload (e.g., confusion, somnolence, edema, etc.)
4) The participant has objective evidence of new or worsening heart failure, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion), including:

    a. Physical examination findings considered to be due to heart failure, including new or worsened:
        i. Peripheral edema
        ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
        iii. Pulmonary rales, crackles, or crepitations

iv. Increased jugular venous pressure and/or hepatojugular reflux
v. S3 gallop
vi. Clinically significant or rapid weight gain thought to be related to fluid retention (usually more than 3-4 lbs in 3-4 days)

b. Laboratory evidence of new or worsening heart failure, if obtained within 24 hours of presentation, including:

i. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP >500 pg/mL or NT-proBNP >2,000 pg/mL). In patients with chronically-elevated natriuretic peptides, a significant (1.25X) increase should be noted above baseline

ii. Radiological evidence of pulmonary congestion

iii**. Non-invasive diagnostic evidence** of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' >15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI)

OR

iv. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mmHg, central venous pressure ≥12 mmHg, or a cardiac index <2.2 L/min/m2

Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

5) The participant receives initiation or intensification of treatment specifically for heart failure, including at least ONE of the following:
   a. Augmentation in oral diuretic therapy
   b. Intravenous diuretic, or vasoactive agent (e.g. positive inotrope, vasopressor or vasodilator)
   c. Mechanical or surgical intervention, including mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
   d. Mechanical fluid removal (e.g., ultrafiltration, Hemofiltration, dialysis)

10.2.2.2 Hospitalization for Myocardial Infarction

Acute MI will be adjudicated when a participant demonstrates at least one of the following biochemical indicators of myocardial necrosis:

• CK-MB greater than 2 x ULN or Troponin I or T greater than 2 x ULN, with a typical pattern of rise and fall consistent with MI

AND at least one of the two following criteria:

• Typical clinical presentation consistent with MI defined as typical cardiac ischemic type pain/discomfort or dyspnea felt to be due to ischemia

OR

• Typical ECG changes consisting of any of the following:
• New abnormal Q waves (or new R waves in lead V1-V2) in at least two consecutive leads
• Evolving, ischemic ST segment or T wave changes in at least two consecutive leads
• New LBBB

10.2.2.3 Hospitalization for Stroke

Stroke is defined as an acute episode of focal or global neurologic dysfunction caused by brain, spinal cord, or retinal vascular injury a result of hemorrhage or infarction. To be classified as a stroke, duration of a focal/global neurological deficit must have a duration >24 hours or imaging confirmation clearly documenting a new hemorrhage or infarct. Events may be classified as a stroke if symptoms were <24 hours due to either pharmacologic or non-pharmacologic interventions or the stroke resulted in death in <24 hours**.**

Classification:

Ischemic Stroke:

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Undetermined Stroke

Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, but with insufficient information to allow categorization as ischemic or hemorrhagic stroke.

10.2.2.4 Other Cardiovascular Hospitalizations

Urgent and unscheduled hospitalizations for other cardiovascular causes that do not meet the criteria for the specific events listed above will be classified as hospitalization for other cardiovascular causes. Examples would include hospitalization for cardiac chest pain that does not meet the criteria for MI, hospitalization for arrhythmias, hospitalization for pulmonary embolism, etc. These hospitalizations will not be further sub-classified by the CEC.

10.2.3 Other Events: Urgent Heart Failure Visit

An urgent heart failure visit is defined as an event that meets all the following:

1) The participant has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of heart failure, but not meeting the criteria for a heart failure hospitalization
2) Signs and symptoms that constitute a heart failure hospitalization [i.e., 3) symptoms, 4) physical examination findings/laboratory evidence of new or worsening heart failure, as indicated above] must be met
3) The participant receives initiation or intensification of treatment specifically for heart failure, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient

10.3 Data and Safety Monitoring Board (DSMB)

The DSMB will be composed of approximately 5 senior academic individuals, including the DSMB Chair. The members will have high-level expertise in cardiology, hematology, clinical research, and statistics. A senior statistician assigned to the trial from the group performing data management services for this trial will oversee the provision of interim data reports for use by the DSMB. The data management group for this trial will transfer pre-agreed datasets to the statistician preparing data for DSMB. During the Open Session of the DSMB meetings, representatives of the SC or Luitpold representatives may present updates on the trial status or the safety profile of FCM, but will not be privy to discussions of the data conducted during the Closed Sessions and will not vote. Proceedings and minutes of the Closed Session will be held in strict confidence and will not be shared outside the DSMB while the trial is ongoing prior to database lock.

The DSMB will be responsible for the interests of the study participants, and to this end, will undertake regular reviews of the safety data. The DSMB will have access to an agreed subset of the study data as listed in the DSMB charter (updated as necessary during the trial) throughout the study duration. In addition, the DSMB will evaluate interim analyses of the data every at least every six months (or on an ad hoc basis if needed) either by face-to-face meeting, or teleconference. The DSMB will determine if it believes the trial should be terminated early because clear evidence exists that either of the two groups has a treatment response that is substantially better than the other.

If the DSMB finds it necessary to recommend actions regarding interruption of the study, or changes to the protocol based on medical rationale that would make it unethical to continue the study in its present form, those recommendations will be forwarded to the SC. The details of the DSMB's functions and the early stopping rules will be delineated in a separate DSMB charter.

INVESTIGATOR'S ACKNOWLEDGEMENT

I have read this protocol and agree to conduct the study as outlined herein, complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR part 312 and all applicable local, state, and federal regulations and International Conference on Harmonisation guidelines.

_____

Investigator's signature

_____

Date

_____

Investigator's Name (Please print)

References

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AMERICAN REGENT, INC.

PROTOCOL

No. 1VIT15043

IND #: 127910

A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Injectafer® (Ferric Carboxymaltose) as Treatment for Heart Failure with Iron Deficiency

SPONSOR

American Regent, Inc.

Clinical Research and Development

800 Adams Avenue, Suite 200

Norristown, PA 19403

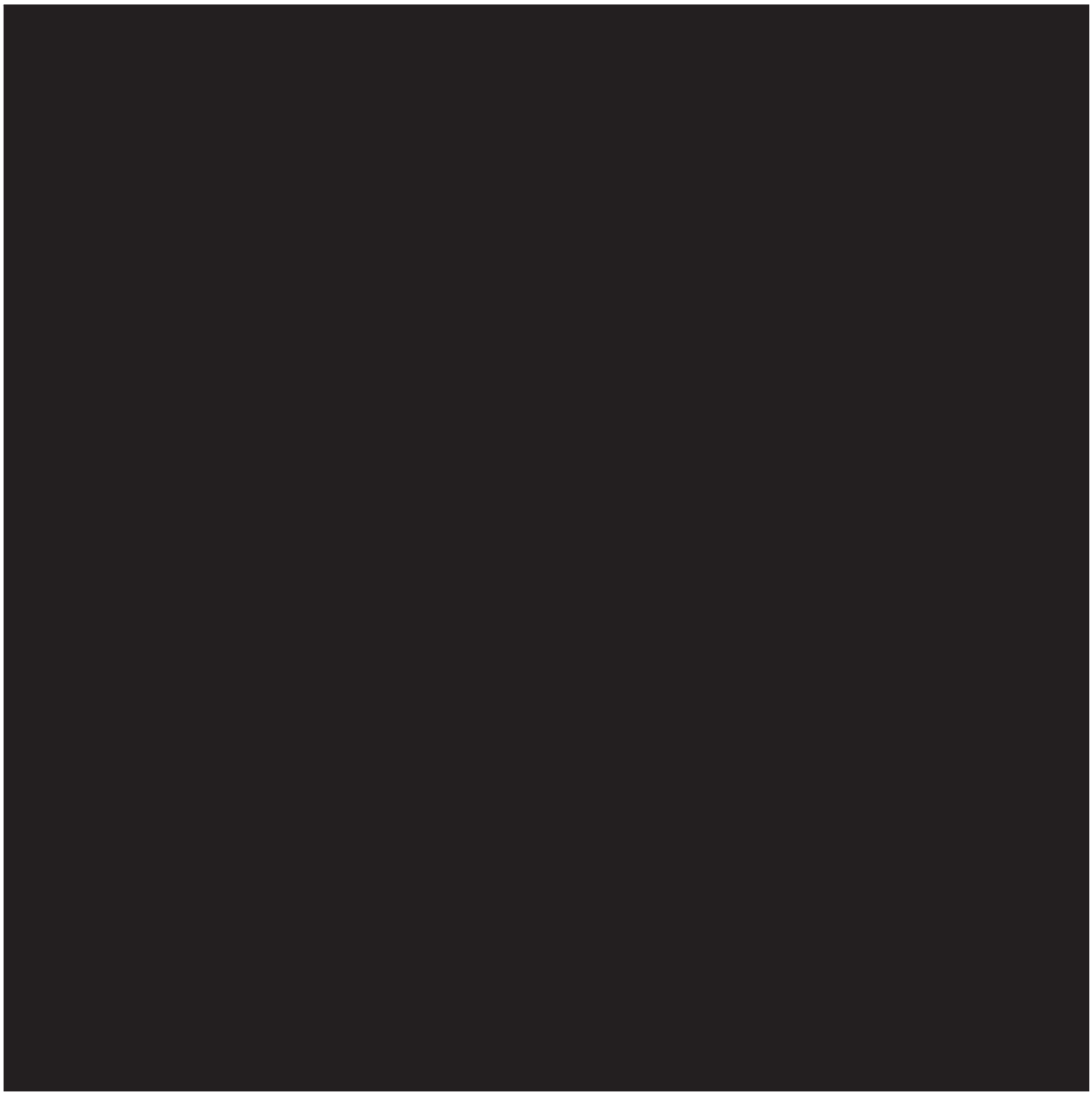
610-650-4200

Protocol Date: 12 January 2017

Version 2 Final Draft Date: 29 November 2018

Version 3 Final Date: 11 January 2021

SIGNATURES OF AGREEMENT FOR PROTOCOL



Study Synopsis

Protocol No. 1VIT15043

Title:	**A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Injectafer® (Ferric Carboxymaltose) as** Treatment for Heart Failure with Iron Deficiency
Study Drug:	Ferric Carboxymaltose (Injectafer®)
Objective:	The primary objective of this study is to determine the efficacy and safety of iron therapy using intravenous (IV) ferric carboxymaltose (FCM), relative to placebo, in the treatment of participants in heart failure with a reduced ejection fraction and with iron deficiency.
Design:	This is a double-blind, multicenter, prospective, randomized, placebo-controlled study to assess the effects of IV FCM compared to placebo on the 12-month rate of death, hospitalization for worsening heart failure, and the 6-month change in 6 minute walk test (6MWT) for patients in heart failure with iron deficiency. After an initial screening period of up to 28 days, eligible participants will be stratified by region and randomized in a 1:1 ratio to FCM or placebo for treatment. Study drug administration will occur on Day 0 and Day 7 (± 2) as an undiluted slow IV push, with additional study visits planned at 3 month intervals, and additional dosing administered every 6 months as applicable (see Section 3.1). For all participants, hematology, ferritin, and transferrin saturation (TSAT), with appropriate safety evaluations, to determine additional treatment, will occur at 6 month intervals. In a subset of sites, a sub-study will be conducted to characterize serum phosphate levels overtime in participants with heart failure and iron deficiency after dosing with FCM (see Appendix 1).

Inclusion Criteria:

1. Adult (≥18 years of age) able to provide signed, written informed consent.
2. Stable heart failure (NYHA II-IV) on maximally-tolerated background therapy (as determined by the site Principle Investigator) for at least 2 weeks prior to randomization.
3. Able and willing to perform a 6MWT at the time of randomization.

4. Reduced left ventricular ejection fraction. Assessment must be performed at least 12 weeks after major cardiac surgical intervention including coronary artery bypass graft (CABG), valvular repair/replacement, or cardiac resynchronization therapy (CRT) device implantation.
    a. Left ventricular ejection fraction ≤40% obtained during the screening visit OR either of the following
        i. Historical value of ejection fraction ≤40% within 24 months of screening visit
        ii. Historical value of ejection fraction ≤30% within 36 months of screening visit
5. Hemoglobin >9.0 g/dL and <13.5 g/dL (females) or <15.0 g/dL (males) within 28 days of randomization.
6. Serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%. Patients with screening ferritin <15 ng/mL must have documentation of an appropriate evaluation, as determined by the Principle Investigator, within 3 months of screening and prior to randomization.
7. Either documented hospitalization for heart failure within 12 months of enrollment or elevated N-terminal-pro-brain natriuretic peptide (NT-proBNP) within 90 days of randomization:
    a. For patients in normal sinus rhythm: N-terminal-pro-brain natriuretic peptide (NT-proBNP) >600 pg/mL (or BNP >200 pg/mL)
    b. For patients in atrial fibrillation: NT-proBNP >1000 pg/mL (or BNP >400 pg/mL

    NOTE: NT-proBNP must be used to confirm eligibility for patients taking sacubitril/valsartan.

Exclusion Criteria:

1. Known hypersensitivity reaction to any component of FCM.
2. History of acquired iron overload, or the recent receipt (within 3 months) of erythropoietin stimulating agent, IV iron therapy, or blood transfusion.
3. Acute myocardial infarction, acute coronary syndrome, transient ischemic attack, or stroke within 30 days of enrollment.
4. Uncorrected severe aortic stenosis, severe valvular regurgitation (except mitral regurgitation due to left ventricular dilatation without planned intervention), or left ventricular outflow obstruction requiring intervention.
5. Current atrial fibrillation or atrial flutter with a mean ventricular response rate >100 per minute (at rest).
6. Current or planned mechanical circulatory support or heart transplantation.
7. Hemodialysis or peritoneal dialysis (current or planned within the next 6 months).

8. Documented liver disease, or active hepatitis (i.e. alanine transaminase or aspartate transaminase >3 times the upper limit of normal range).
9. Current or recent (within 3 years) malignancy with exception of basal cell carcinoma or squamous cell carcinoma of the skin, or cervical intraepithelial neoplasia.
10. Active gastrointestinal bleeding.
11. Female participant of child-bearing potential who is pregnant, lactating, or not willing to use adequate contraceptive precautions during the study and for up to 5 days after the last scheduled dose of study medication.
12. Inability to return for follow up visits within the necessary windows
13. Concurrently in a study with investigational product.
14. Current COVID-19 infection.

Study Drug Administration

Initial treatment will occur on Day 0 (date of randomization) and Day 7. On Day 0 and Day 7, Group A (FCM) will receive a 750 mg undiluted blinded dose of IV FCM at the rate of approximately 100 mg (2 mL)/minute; Group B (placebo) will receive a blinded placebo (15 cc of normal saline) IV push at 2 mL/minute. Participants in Group A with body weight <50 kg (110 pounds) will have individual FCM doses adjusted to 15 mg/kg, not to exceed an individual dose of 750 mg, or a cumulative dose of 1500 mg per treatment cycle.

All participants will be dosed every 6 months for the duration of the trial. Participants randomized to the FCM arm will be dosed as indicated based on hemoglobin (Hgb) levels (i.e. Hgb <13.5 g/dl [females] or <15.0 g/dl [males)]) and iron studies (i.e. serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%). Participants not meeting post- randomization lab criteria for blood counts and iron studies and all participants randomized to the placebo arm will be administered IV placebo at each visit.

Unblinded site personnel, responsible for preparation and administration of the FCM or Placebo, will ensure that the participant and all blinded site staff are not able to observe the preparation or administration of study treatment.

Patient Assessments

Efficacy and Safety Follow-up: All participants will be followed from the time of randomization until completion of the trial. The last participant randomized will be followed for 12 months. After treatment on Day 0 and Day 7, participants will be evaluated at 3 month intervals (in person or via telephone), with additional dosing administered every 6 months as applicable (see Section 3.1). Hematology, ferritin, and transferrin saturation (TSAT) laboratory assessments will be performed in all participants, with appropriate safety evaluations, to determine if additional treatment will occur at 6 month intervals. At the conclusion of the study all participants will be assessed for the occurrence of any potential endpoint or serious adverse events. Attempts to determine Vital Status, including endpoint ascertainment, for participants who are lost to follow-up or withdrawn will be made via a search of available public records, and other appropriate investigative techniques, including the potential use of third party vendors as described in the informed consent form and in accordance with applicable regulatory requirements.

Primary Endpoint:

Hierarchical composite of 1) death, 2) hospitalization for heart failure (defined in Section 10.2), or 3) change in 6MWT. (Death and hospitalizations for heart failure will be evaluated at one year, Change in 6MWT will be evaluated at 6 months) and tested using the nonparametric Wilcoxon-type test.

Secondary Endpoints

1. Time to first event of the composite of cardiovascular death or heart failure hospitalization. The composite endpoint will be composed of adjudicated occurrence (as defined in Section 10.2) of one of the following:

    a. Cardiovascular Death
        i. Death due to Heart Failure
        ii. Death due to Acute Myocardial Infarction
        iii. Sudden Cardiac Death
        iv. Death due to Stroke
        v. Death due to other Cardiovascular Causes
    b. Hospitalization for Worsening Heart Failure

2. Mean change in 6MWT from baseline to 12 months
3. Time to first event of the composite of cardiovascular death or intervention for worsening heart failure (hospitalization or urgent heart failure visits)
4. Time to first event of the composite of cardiovascular death and cardiovascular hospitalizations

5. Time to cardiovascular death

Additional events to be adjudicated for analysis of the secondary endpoints include:

a) Non-cardiovascular death
b) Hospitalization for myocardial infarction
c) Hospitalization for stroke
d) Other cardiovascular hospitalizations
e) Urgent heart failure visits

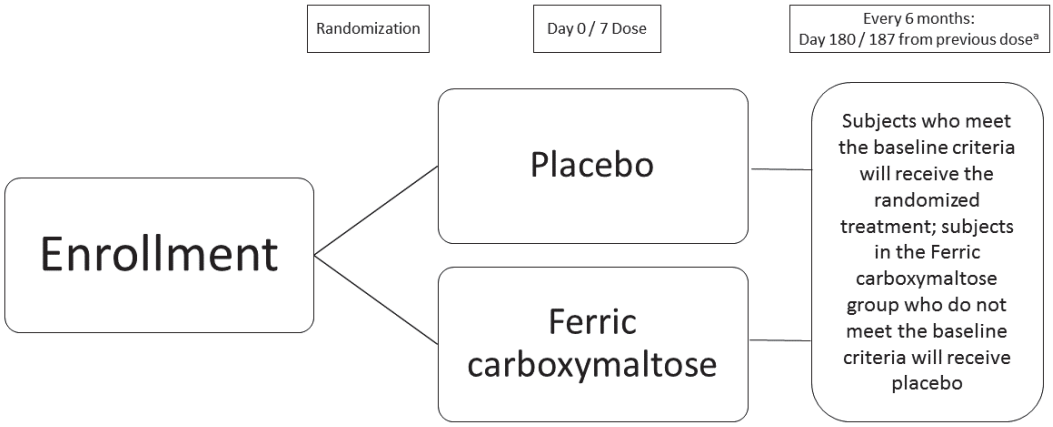
All events are operationally defined in Section 10.2. Events will be confirmed by the Clinical Events Classification (CEC) Committee of the Duke Clinical Research Institute (DCRI)

Study duration per participant: Screening Phase: up to 28 days prior to randomization.
Post randomization phase: Variable with a minimum of 365 Days.

Study Sites: Approximately 300

Participant Number: Approximately 3014

Figure 1. Study Diagram



[a] All participants will be dosed every 180 and 187 days from their previous dose for the entire study duration. Randomized treatment will be administered if hemoglobin <13.5 g/dl (females) or <15.0 g/dl (males) and serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%; placebo will be administered to participants in the Ferric carboxymaltose group who do not meet the above criteria.

LIST OF ABBREVIATIONS

6MWT	Six Minute Walk Test
AE	Adverse event
ALT	Alanine Aminotransferase
AST	Aspartate aminotransferase
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
BUN	Blood urea nitrogen
CABG	Coronary Artery Bypass Grafting
cc	cubic centimeter
CEC	Clinical Events Classification
CFR	Code of Federal Regulations
CI	Confidence Interval
CKD	Chronic Kidney Disease
CK-MB	Creatine Kinase-Myocardial Band
cm	Centimeter
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CV	Cardiovascular
DCRI	Duke Clinical Research Institute
dL	Deciliter
DSMB	Data and Safety Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
e.g.	For example
EOS	End of Study
EU	European Union
FCM	Ferric Carboxymaltose
FDA	Food and Drug Administration
Fe	Iron
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
Hct	Hematocrit
HF	Heart Failure
Hg	Mercury
Hgb	Hemoglobin
ICD	Implantable Cardioverter-Defibrillator
ICH	International Conference on Harmonisation
i.e.	that is
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous

IRT	Interactive Response Technology
ITT	Intention to Treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
Kg	Kilogram
L	Liter
LBBB	Left Bundle-Branch Block
LDH	Lactic dehydrogenase
LVEF	Left Ventricular Ejection Fraction
LVOT	Left Ventricular Outflow Tract
MB	Myocardial b Fraction
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
m	Meter
mg	Milligram
MHRA Agency	Medicines and Healthcare Products Regulatory
MI	Myocardial Infarction
mL	Milliliter
ng	Nanogram
NS	Normal Saline
NT-proBNP	N-Terminal Prohormone of Brain Natriuretic Peptide
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
pg	Picogram
PGA	Patient Global Assessment
PTH	Parathyroid Hormone
RBC	Red blood cell
RDW	Red (cell) distribution width
SAE	Serious Adverse Event
SC	Steering Committee
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
TVI	Time Velocity Integral
ULN	Upper Limit of the Normal
US	United States
USP	United States Pharmacopeia
UK	United Kingdom
WBC	White Blood Cell
w/v	weight / volume

1.0 INTRODUCTION

1.1 Heart Failure with Iron Deficiency

Over 5 million people in the United States (US) live with heart failure. Epidemiological studies in heart failure suggest a 50% prevalence of either absolute iron deficiency, defined as serum ferritin <100 ng/mL, or functional iron deficiency, defined as a ferritin 100 to 300 ng/mL with transferrin saturation (TSAT) <20% [van Veldhuisen 2011; Ebner 2013]. The prevalence of iron deficiency increases with the severity of heart failure and etiologies include insufficient dietary iron, poor iron absorption, gastrointestinal blood loss, chronic disease, and repeated blood sampling for ongoing medical evaluation of heart failure and comorbid conditions.

Alteration in iron homeostasis has been identified as an independent risk factor for mortality in patients with heart failure [Okonko 2011; Jankowska 2013]. It is hypothesized that reduced oxygenation, combined with insufficient iron for appropriate oxygen transportation and storage, may have additive untoward effects on oxidative metabolism and cellular immune mechanisms in this population. Iron deficiency may also increase the risk of thrombosis and mortality among patients in heart failure with iron deficiency [Streja 2008].

1.2 Treatment of Iron Deficiency in Heart Failure

Evidence in support of the therapeutic value of intravenous (IV) iron repletion with ferric carboxymaltose (FCM) for patients in heart failure with a reduced ejection fraction and iron deficiency is provided by 4 European studies: FER-CARS-01, FER-CARS-02 (FAIR-HF), FER-CARS-03 (EFFICACY-HF), and FER-CARS-05 (CONFIRM-HF). In addition to measures of iron repletion and hemoglobin changes, these studies focused on changes from baseline in New York Heart Association (NYHA) functional class, Patient Global Assessment (PGA), and the 6-minute walk test (6MWT).

In the most recent of the studies, CONFIRM HF, a total of 301 participants (150 FCM, 151 placebo) were treated for up to 52 weeks (longest duration among the 4 studies). The primary efficacy analysis confirmed the benefit of FCM relative to placebo for the improvement in 6MWT distance at Week 24, with a comparative difference (FCM versus placebo) in the change from baseline reported as least squares mean (± standard error) of 33.2 ± 10.52 m (p=0.002). The treatment benefit of FCM versus placebo in 6MWT distance was sustained through to Week 52 ($p \leq 0.001$) and was consistent across subgroups. Commensurate with the improvement in 6MWT distance, improvements in PGA, NYHA functional class, overall Kansas City Cardiomyopathy Questionnaire (KCCQ) score, and fatigue score were seen in FCM-treated participants as compared to placebo-treated participants. Treatment with FCM versus placebo was also associated with a significant reduction in the risk of hospitalization due to worsening heart failure (hazard ratio: 0.40; 95% confidence interval [CI]: 0.2 to 0.8; p=0.009) and a significant reduction in the risk of first hospitalization due to worsening heart failure or all-cause death (hazard ratio: 0.53; 95% CI: 0.30 to 0.95; p = 0.03). Similar trends for reduction in hospitalization were reported for FCM and iron sucrose [Kapoor 2013].

A meta-analysis of these four trials was conducted to assess the association of FCM exposure with morbidity and mortality [Anker 2015]. The analysis included individual participant pooled data for 839 participants, 504 of whom with FCM exposure versus 335 with placebo exposure. The primary endpoint was defined as the composite outcome of cardiovascular death and cardiovascular hospitalization. Participants randomized to FCM had a lower rate of cardiovascular death and cardiovascular hospitalization compared to placebo, with a rate ratio of 0.59 (95% CI: 0.40 to 0.88; p=0.009) in a recurrent events analysis. Additionally, exposure to FCM was associated with reduced cardiovascular death and hospitalization for heart failure, with a rate ratio of 0.53 (95% CI: 0.33 to 0.86; p=0.011) and all-cause death and cardiovascular hospitalization, with a rate ratio of 0.60 (95% CI: 0.41 to 0.88; p=0.009).

The four European trials, together with the meta-analysis, suggest that IV iron repletion as treatment for patients in reduced left ventricular ejection fraction with iron deficiency is associated with improvement in functional health (the 6MWT), patient-reported outcomes, morbidity defined as cardiovascular hospitalization, and mortality. Given that FCM is approved by the US Food and Drug Administration (FDA) for use in iron-deficiency anemia [US Package Insert], a clinical development program is proposed seeking FDA approval for FCM as treatment for patients in heart failure with reduced ejection fraction who have iron deficiency.

1.3 Injectafer® (Ferric Carboxymaltose)

1.3.1 Key Features of Ferric Carboxymaltose

Injectafer® (FCM) is a stable Type I polynuclear iron (III)-hydroxide carbohydrate complex developed as an IV iron replacement therapy for the treatment of iron deficiency anemia. After IV administration, FCM is mainly found in the reticuloendothelial system which includes the liver, spleen, and bone marrow. The iron slowly dissociates from the complex and can be efficiently used in the bone marrow for hemoglobin synthesis. The carbohydrate moiety of FCM is metabolized by the glycolytic pathway. FCM is approved for the treatment of iron deficient anemia, and is an investigational product in this study for patients in heart failure with iron deficiency.

1.3.2 Injectafer® versus Other Parenteral Iron Agents

There is considerable efficacy and safety experience with the various available parenteral iron preparations. However, prior to the approval of non-dextran formulations, the risk of systemic adverse reactions restricted IV iron use. The use of FCM offers significant advantages compared to other available IV iron preparations. Due to its structure, Injectafer® is more stable than iron gluconate and iron sucrose resulting in a slow delivery of the complexed iron to endogenous iron binding sites. In animals, FCM has approximately 1/5th the acute toxicity that has been reported for iron sucrose. These characteristics of FCM make it possible to administer much higher single doses over shorter periods of time than iron gluconate or iron sucrose, resulting in fewer administrations to replenish iron stores, and convenient outpatient use. In the EU, ferumoxytol has been withdrawn from use and in the US, it has been given a black box warning.

1.3.3 Injectafer® Human Experience

The Injectafer® clinical development program demonstrated the effectiveness and safety of Injectafer® in the treatment of iron-deficiency anemia. The drug is approved for the treatment of iron deficiency anemia in adult populations who have intolerance to oral iron, have had unsatisfactory responses to oral iron, or who have non-dialysis dependent CKD. Clinical data are currently available from 20 Phase 2 and 3 studies including 5,799 patients, with iron deficient anemia or iron deficiency anemia associated with CKD who received Injectafer®

A clinical pharmacokinetic study (VIT-IV-CL-001) using positron emission tomography demonstrated a fast initial elimination of radioactively labeled iron (Fe) $^{52}Fe/^{59}Fe$ Injectafer (FCM) from the blood, with rapid transfer to the bone marrow and rapid deposition in the liver and spleen. Eight hours after administration, 5 to 20% of the injected amount of radioactively-labeled Fe was still detected in the blood.

Important details of pre-clinical safety and efficacy and clinical safety and efficacy can be found in the Investigator's Brochure. Ferric carboxymaltose received approval from the United Kingdom (UK) Medicines and Healthcare Products Regulatory Agency (MHRA) on June 15, 2007 (EU Trade name: Ferinject). Injectafer® now has marketing authorization in 70 countries, and is currently marketed in 61 of these countries. Injectafer® received approval for the treatment of iron-deficiency anemia from the US (FDA) on July 25, 2013.

2.0 TRIAL OBJECTIVE

2.1 Primary Objective

To determine the efficacy and safety of iron therapy using intravenous (IV) FCM, relative to placebo, in the treatment of patients in heart failure with reduced ejection fraction and with iron deficiency.

2.2 Secondary Objective

To evaluate the effect of IV FCM, relative to placebo, on the functional capacity of patients in heart failure with reduced ejection fraction and with iron deficiency.

3.0 OVERALL STUDY DESIGN AND RATIONALE

3.1 Overall Study Design

This is a double-blind, multicenter, prospective, randomized, placebo-controlled study to assess the effects of IV FCM compared to placebo on the 12-month rate of death and hospitalization for worsening heart failure, and change in 6MWT at 6 month for patients in heart failure with reduced ejection fraction and with iron deficiency.

After an initial screening period of up to 28 days, eligible participants will be stratified by region and randomized in a 1:1 ratio to FCM or placebo. Study drug administration will occur on Day 0 and Day 7 as an undiluted slow IV push, with additional study visits (in

person or via telephone) planned at 3 month intervals, and additional dosing administered every 6 months as applicable (based on dose regimen below). For all participants, hematology, ferritin and transferrin saturation (TSAT), with appropriate safety evaluations, to determine additional treatment, will occur at 6 month intervals.

In a subset of sites, a sub-study will be conducted to characterize serum phosphate levels overtime in participants in heart failure with iron deficiency after dosing with FCM (see Appendix 1).

Initial treatment will occur on Day 0 and Day 7. On Day 0 and 7, Group A (FCM) will receive a 750 mg undiluted, blinded dose of IV FCM at the rate of approximately 100 mg (2 mL)/minute; Group B (placebo) will receive a blinded placebo (15 cc of normal saline) IV push at 2 mL/minute. Participants in Group A with body weight <50 kg (110 pounds) will have individual FCM doses adjusted to 15 mg/kg, not to exceed an individual dose of 750 mgs or a cumulative dose of 1500 mg per treatment cycle. Placebo dosing will be adjusted for weight based on volume.

All participants randomized will be dosed every 6 months. Participants randomized to the FCM arm will be dosed as indicated based on hemoglobin levels (i.e. Hgb <13.5 g/dL [females] or <15.0 g/dL [males)]) and iron studies (i.e. serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%). Participants not meeting pre-specified laboratory criteria for blood counts and iron studies and all participants randomized to the placebo arm will be administered IV placebo infusion at each visit.

Unblinded site personnel, responsible for preparation and administration of the FCM or Placebo, will ensure that the participant and all blinded site staff are not able to observe the preparation or administration of study treatment.

3.2 Rationale of Study Design and Choice of Control Groups

Since FCM is being studied as a treatment for heart failure patients with a reduced ejection fraction and comorbid iron deficiency, it is important to establish its efficacy and safety in terms of clinically significant endpoints including cardiovascular morbidity.

This study will assess the efficacy and safety of FCM as a treatment for participants in heart failure with reduced ejection fraction and concomitant iron deficiency by comparing the proposed regimen to placebo (normal saline). The placebo arm is justified as participants will be maintained on the maximally tolerated background therapy for heart failure with a reduced ejection fraction.

3.3 Schedule of Events

Study Procedures	Screening	Treatment Phase		Follow-up Phase				
Days	-28 to -1	0	7±2	90 ±14[a,b,,l]	160-176 [a,b]	180±7 [a,b]	187 ±7 [a,b]	EOS[c]
Informed consent	X							
Inclusion/exclusion criteria	X	X[j]						
Demographics	X							
Targeted medical history	X							
Targeted Physical Exam		X[j]						X
Vital signs		X[d]	X[d]			X[d]	X[d]	X
Height (cm) & weight (kg)		X[ej]				X[e]		
Urine or serum pregnancy test		X[fj]				X[f]		X[f]
1,25 $(OH)_2$ Vitamin D, 25 (OH) Vitamin D and PTH[k]		X[k]			X[k]			
Left ventricular ejection fraction	X[g]							
Randomization		X[n]						
Hematology laboratory	X[hp]	X[h]			X[h]			X[h]
Chemistry laboratory		X[h]			X[h]			X[h]
Iron indices	X[h]	X[h]			X[h]			X[h]
6 Minute Walk Test		X[j]				X[m]		
NT-proBNP	X[h]	X[h]			X[h]			X[h]
Serious Adverse Event and Clinical Endpoint Event reporting		X	X	X	X	X	X	X
Concomitant medications	X	X	X			X	X	X
IV FCM/ IV Placebo		X[n]	X[n]			X[in]	X[in]	

Abbreviations: EOS = End of Study; FCM = ferric carboxymaltose; IV = intravenous; NT-proBNP = N-terminal pro-brain natriuretic peptide; PTH = Parathyroid Hormone;

a Visits will be repeated every 180 days for the duration of the study

b At end of study, the visit should not be performed if it would occur within 30 days of the EOS visit. If the participant is prematurely discontinued from the study and completing the EOS visit, the regular 6 or 12 month visit is needed to obtain the 6MWT.

c EOS visit for all participants will be scheduled once the last participant has reached 12 months on study and the anticipated number of outcome events (Section 8) reaches 771.

d On study drug dosing days vital signs will be collected predose, immediately postdose, and 30 minutes postdose. Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.

e Height assessed at Day 0 only; weight assessed at Day 0 and prior to each dosing cycle.

f. Females of childbearing potential

g. Historical value can be used if performed within 24 months of screening visit (or 36 months if LVEF ≤30%), must be performed at least 12 weeks after major cardiac intervention-including CABG, valvular intervention, or cardiac resynchronization therapy device implantation.

h. The method of analysis of screening laboratory values will be by a central clinical laboratory. All visits will be analyzed through a central laboratory
i All participants randomized will be dosed every 6 months. Participants randomized to the FCM arm will be dosed as indicated based on blood counts (i.e. Hgb <13.5 g/dL [females] or <15.0 g/dL [males)]) and iron studies (i.e. serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%). Participants not meeting pre-specified laboratory criteria for blood counts and iron studies and all participants randomized to the placebo arm will be administered IV placebo infusion at each visit. The second of the 2 dosing visits should occur at Day 7±2 after the first dose.
j. Prior to randomization
k Only for participants at select sites performing additional chemistry labs ($1,25\ (OH)_2$ Vitamin D, 25 (OH) Vitamin D and PTH) (sub-study).
l. May be performed via telephone or in person.
m. Performed at Day 180 and Day 360 visits only.
n. To be performed by unblinded site personnel. All other procedures must be performed by personnel blinded to the treatment assignment
p, Hemoglobin only

4.0 PARTICIPANT SELECTION

4.1 Number and Type of Participants

The study cohort will comprise approximately 3,014 participants in heart failure with iron deficiency who fulfill the inclusion criteria, do not meet any of the exclusion criteria, and who have given written informed consent.

4.2 Screening Phase

Once a participant signs the informed consent document and enters the screening phase, a unique screening number will be assigned via an interactive response technology (IRT) system.

4.2.1 Inclusion Criteria

1. Adult (≥18 years of age) able to provide signed, written informed consent.
2. Stable heart failure (NYHA II-IV) on maximally-tolerated background therapy (as determined by the site Principle Investigator) for at least 2 weeks prior to randomization.
3. Able and willing to perform a 6MWT at the time of randomization.
4. Reduced left ventricular ejection fraction. Assessment must be performed at least 12 weeks after major cardiac surgical intervention including coronary artery bypass graft (CABG), valvular repair/replacement, or cardiac resynchronization therapy (CRT) device implantation.
    a. Left ventricular ejection fraction ≤40% obtained during the screening visit OR either of the following
        i. Historical value of ejection fraction ≤40% within 24 months of screening visit

ii. Historical value of ejection fraction ≤30% within 36 months of screening visit

5. Hemoglobin >9.0 g/dL and <13.5 g/dL (females) or <15.0 g/dL (males) within 28 days of randomization.
6. Serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%. Patients with screening ferritin <15 ng/mL must have documentation of an appropriate evaluation, as determined by the Principle Investigator, within 3 months of screening and prior to randomization.
7. Either documented hospitalization for heart failure within 12 months of enrollment or elevated N-terminal-pro-brain natriuretic peptide (NT-proBNP) within 90 days of randomization:
    a. For patients in normal sinus rhythm: N-terminal-pro-brain natriuretic peptide (NT-proBNP) >600 pg/mL (or BNP >200 pg/mL)
    b. For patients in atrial fibrillation: NT-proBNP >1000 pg/mL (or BNP >400 pg/mL

    NOTE: NT-proBNP must be used to confirm eligibility for patients taking sacubitril/valsartan.

4.2.2 Exclusion Criteria

1. Known hypersensitivity reaction to any component of FCM.
2. History of acquired iron overload, or the recent receipt (within 3 months) of erythropoietin stimulating agent, IV iron therapy, or blood transfusion.
3. Acute myocardial infarction, acute coronary syndrome, transient ischemic attack, or stroke within 30 days of enrollment.
4. Uncorrected severe aortic stenosis, severe valvular regurgitation (except mitral regurgitation due to left ventricular dilatation without planned intervention), or left ventricular outflow obstruction requiring intervention.
5. Current atrial fibrillation or atrial flutter with a mean ventricular response rate >100 per minute (at rest).
6. Current or planned mechanical circulatory support or heart transplantation.
7. Hemodialysis or peritoneal dialysis (current or planned within the next 6 months).
8. Documented liver disease, or active hepatitis (i.e. alanine transaminase or aspartate transaminase >3 times the upper limit of normal range).
9. Current or recent (within 3 years) malignancy with exception of basal cell carcinoma or squamous cell carcinoma of the skin, or cervical intraepithelial neoplasia.
10. Active gastrointestinal bleeding.

11. Female participant of child-bearing potential who is pregnant, lactating, or not willing to use adequate contraceptive precautions during the study and for up to 5 days after the last scheduled dose of study medication.
12. Inability to return for follow up visits within the necessary windows
13. Concurrently in a study with an investigational product.
14. Current COVID-19 infection.

4.3 Participant Assignment and Randomization Process

Participants who meet all inclusion requirements and no exclusionary criteria will be offered enrollment in this study. Enrolled participants will be stratified by region and randomized in a 1:1 ratio to receive either IV FCM or IV Placebo.

The FCM Group will initially receive 2 blinded doses of FCM at 15 mg/kg to a maximum of 750 mg per dose for a maximum total dose of 1500 mg.

The Placebo Group will receive 2 blinded doses of 15 mL of normal saline.

Participants and blinded study staff will remain blinded to the treatment assignment for the duration of the study.

4.4 Withdrawal from Study

Any participant who wishes to withdraw from the study may do so at any time without the need to justify their decision. The investigator may withdraw a participant from active study treatment at any time if it is felt to be in the best interest of the participant

At time of withdrawal from the study, procedures for the Termination visit must be immediately performed regardless of whether the participant has completed study drug treatment. Information collected previously as part of the study will be retained unless the patient specifically withdraws consent, in writing. The participant should be contacted at the end of the study to assess for the occurrence of any potential endpoint events. Additionally, if the participant cannot be contacted, attempts to determine the Vital Status will be performed via a search of available public records, third party vendor search, medical record review, additional contacts provided by the patient, and other appropriate investigative techniques as described in the informed consent form and in accordance with applicable regulatory requirements.

In event of site closure, participants may be asked to agree to follow up at another research site, if available, or for follow up by a patient follow-up group.

4.5 Discontinuation from Study Drug

Participants may elect to discontinue study drug, but wish to remain in the study for follow-up. In those situations, patients will be asked to continue the normal clinical trial schedule for ascertainment of endpoint and safety events. Participants who discontinue study drug for reasons unrelated to safety may resume study drug if deemed appropriate by the Principal Investigator.

If a participant permanently discontinues investigational product (drug is considered to be permanently discontinued after the second missed dosing cycle with continued follow-up in the trial) and is unable to attend visits in-person, he/she will be contacted by telephone, or other methods to assess study outcomes and vital status, unless the participant has specifically withdrawn consent for all forms of contact. Every effort should be made to educate the participants on the importance of remaining in the study and attending scheduled study visits including those required after early discontinuation of investigational product. Other participant follow-up options to collect study outcomes and vital status should be pursued according to local laws and regulations. If one of these alternate methods to collect study outcomes and vital status is acceptable to the participant, then the participant will be deemed not to have withdrawn consent for follow-up.

4.6 Participants Deemed Lost to Follow-up

Investigators should make every effort to contact participants who are deemed lost to follow-up and who have not withdrawn consent to follow-up contacts, including medical record review, pursuing any alternative contact methods permitted by local regulations. Where permitted, a third party may be used to locate alternative participant contact information that will be provided to the investigator. All attempts to contact participants will be documented in the participant's source notes.

Should a participant fail to attend the clinic for a required study visit, the site should attempt to contact the participant and re-schedule the missed visit as soon as possible. The site should also counsel the participant on the importance of maintaining the assigned visit schedule. In cases where the participant does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the participant. Should the participant continue to be unreachable, then and only then, will he/she be considered "Lost to Follow-up." Nonetheless, efforts to attempt to locate and contact the participant, and to ascertain the participant's vital status will continue until trial completion.

4.7 Concomitant Intervention

Concomitant intervention is defined as follows:

- Blood transfusion.
- Use of IV iron outside of protocol.

When concomitant intervention occurs, the date of the intervening event should be recorded in the source documents, and the eCase Report Form (eCRF). The participant should continue in the study as scheduled.

5.0 STUDY DRUG

5.1 Formulation, Packaging and Storage

All investigational medication to be used in this study [supplied by American Regent, Inc.] will have been prepared according to Good Manufacturing Practices (GMP).

FCM (trade name, Injectafer®) will be supplied as 15 ml vials, containing 750 mg of iron as 5% w/v iron containing a polynuclear iron(III)-hydroxide 4(R)–(poly-(1-->4)-*O* α -D-glucopyranosyl)-oxy-2 (R), 3(S), 5(R), 6-tetrahydroxy-hexonate complex in a solution of water for injection [50 mg/ml] and will be labeled according to FDA investigational regulatory requirements.

Placebo (normal saline) will be supplied as 15 ml fill in 20 ml vials.

All IV study drugs (FCM and Normal Saline) must be kept in a secure place at the investigational site, and stored at room temperature (see USP). The study medication should not be frozen. Vials may not be used for more than 1 dose, or for more than 1 participant. All vials (used and unused) should be kept by the study staff for reconciliation by the monitor unless the site is unable to retain them and documentation (site or institution process or procedures, or SOPs, for example) is present. Following reconciliation, sites may destroy used and unused study drug on site using local procedures, provided a drug destruction policy is in place, or it may be returned to American Regent, Inc.

5.2 Drug Administration/Regimen

The Principal Investigator or designee will supervise administration of the study drug to participants. The participants should remain blinded to the identity of the study drug for the duration of the trial.

Group A: Group A (FCM) will receive a 750 mg undiluted blinded dose of IV FCM at the rate of approximately 100 mg (2 mL)/minute (approximately 7 minutes 30 seconds) on Day 0 and Day 7, not to exceed an individual dose of 750 mg or a cumulative dose of 1500 mg per treatment cycle.

Group B: Group B (placebo) will receive a blinded placebo (15 cc of normal saline) IV push at 2 mL/minute (approximately 7 minutes 30 seconds) on Day 0 and Day 7.

Note: To avoid unblinding on the dose administration worksheet, if a participant is under 50 kg (110 pounds), the volume of FCM or placebo administered should be calculated based on the participant's weight, e.g. a 45 kg participant will receive a 13.5 mL dose of FCM or placebo.

All participants will be dosed every 6 months. At each 6-month interval, 2 doses of study drug will be administered as described above for Day 0 and Day 7. The same randomized treatment will be administered if Hgb <13.5 g/dL (females) or <15.0 g/dL (males) and serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%; placebo will be administered to participants in the FCM group who do not meet the above criteria.

Site personnel will ensure the participant and blinded study staff are not able to observe the preparation or administration of study treatment injections.

5.3 IV Medication Precautions

When administering FCM or Placebo, the following precautions will be taken:

- The participant will be evaluated clinically prior to drug administration to assess the development of clinically significant conditions.
- The vials will be visually inspected for particulate matter and discoloration before use. If noted, the vial will not be used, and the Investigator or his designee will notify the sponsor or sponsor's designee for replacement of the study drug, and for direction on the return of the unused vial.
- Heart rate and blood pressure will be assessed pre-, immediately post, and 30 minutes post administration. Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.
- The participant will be monitored for at least 30 minutes for serious acute reactions as hypersensitivity or bioactive (labile) iron reactions to non-dextran IV iron products have rarely been reported. The reactions include: hypotension, loss of consciousness, bronchospasm with dyspnea, shortness of breath, and seizures.
    - In the event a serious acute reaction is seen, the site must have the capability to provide appropriate resuscitation measures. These may include IV NS, IV epinephrine, steroids, and/or antihistamines.

5.4 Drug Accountability

Investigators will keep records of the receipt, administration and return of the study drug (FCM). They will not allow the study drug to be used for purposes other than as directed by this protocol. The investigator agrees that he/she will not supply study medication to any persons other than those randomized in the study, or to investigators not listed on the FDA 1572. When the study is completed, or if it is prematurely terminated, a final inventory of all clinical supplies must be compiled and the remainder of the unused study drug will be returned to American Regent, Inc., or destroyed on site, per the site's documented locally accepted policies. All data regarding the study drug must be recorded as per the Monitoring Plan.

5.5 Concomitant Medication

All Concomitant medications will be recorded in the eCase Report Form (eCRF).

Note: Oral iron supplementation is permitted prior to screening and during the course of the study.

No prophylactic medications specifically for administration of study drug may be administered prior to study drug administration without prior approval from American Regent, Inc. Other standard therapies are permitted.

5.6 Blinding

All participants and blinded study staff will be blinded to the content of study drug for the duration of the trial.

During the period of study drug administration, the blinded personnel will not be with the subject or in a location that could result in the blind being inadvertently broken. However, the Principal Investigator or designee will be available in the event of an emergency, and/or the need for adverse event assessment. All blinded study personnel will be blinded to the post-treatment iron indices and serum phosphorous laboratory results, as the values may break the blind.

The blinding will be maintained until the study is complete, and the database has been locked. In the event of an emergency that would require the investigator to be aware of the treatment allocation prior to database lock, the investigator can obtain this information, on a per participant basis. **It is recommended to contact the sponsor's Medical Monitor or designee prior to unblinding.** If a participant's treatment assignment is unblinded, the sponsor must be contacted immediately via telephone.

6.0 STUDY PROCEDURES

6.1 Informed Consent

Prior to any study specific procedures, the investigator or his or her designee must explain to each participant the nature of the study, its purpose, procedures to be performed, expected duration, and the benefits and risks of study participation. After this explanation the participant must voluntarily sign an informed consent statement (Required Elements of Informed Consent, 21 CFR 50.25). The participant will be given a copy of the signed consent form.

6.2 Screening Phase (Day -28 to Day 0)

6.2.1 Screening Visit

Each participant who has signed the informed consent and qualifies for inclusion will undergo the following clinical evaluations to confirm eligibility for the study (all procedures to be performed by blinded study personnel):

- Demographic and medical history including NYHA heart failure class and prior heart failure hospitalizations

- Left ventricular ejection fraction (historical values may be used if performed within 24 months of the screening visit, or 36 months if LVEF ≤30%) must be performed at least 12 weeks after major cardiac intervention-including CABG, valvular intervention, or cardiac resynchronization therapy device implantation
- Blood samples for hematology, iron indices, and NT-proBNP (central laboratory)
- Concomitant medications
- Review inclusion/exclusion criteria
- Enter participant in the Interactive Response Technology (IRT) system to obtain screening number.

Participants who do not meet study entry criteria should be entered into the IRT system as a screen failure.

6.3 Treatment Phase (Day 0 to Day 7)

6.3.1 Day 0 Visit

All eligible participants will be randomized to either Group A or Group B in a 1:1 ratio based on a pre-determined randomization schedule via an IRT system.

The following will be obtained and/or completed before contacting IRT for randomization:

For all participants (all procedures to be performed by blinded study personnel):

- Verify all inclusion and exclusion criteria
- Height and weight
- Targeted physical exam
- Blood samples for central lab hematology, chemistries and iron indices for all participants; For Hypophosphatemia Sub-Study participants only: 1,25 $(OH)_2$ Vitamin D, 25 (OH) Vitamin D and PTH.
- Review concomitant medications
- Urine or serum pregnancy test (women of childbearing potential only)
- Administer 6MWT per standardized procedure

The IRT system will then be contacted by an **Unblinded** study team member and all eligible participants will be randomized to either Group A or Group B in a 1:1 ratio with stratification by region based on a pre-determined randomization schedule. After assignment of the treatment group the following will occur:

Note: To avoid unblinding on the dose administration worksheet, if a participant is under 50 kg, the volume of FCM or placebo administered should be calculated based on the participant's weight, e.g. a 45 kg participant will receive a 13.5 mL dose of FCM or placebo.

Note: All IV injection start and stop times should be captured in hh:mm:ss format.

Group A:

- Verify amount of single FCM dose (15 mg/kg up to a maximum dose of 750 mg) (unblinded staff)

- Pre-administration, obtain heart rate, blood pressure, and body temperature (blinded staff)
- Administer FCM as a slow IV injection at the rate of approximately 2 mL /minute taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff).
- Document start and stop time of FCM administration and the total dose and volume administered (unblinded staff)
- Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after FCM administration (blinded staff). Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.
- Adverse event / serious adverse event assessment (starting at beginning of FCM injection) (blinded staff)

Group B:

- Pre-administration, obtain heart rate, blood pressure, and body temperature (blinded staff)
- Administer a 15 mL dose of placebo (normal saline) as a slow IV injection at the rate of approximately 2 mL /minute taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff).
  - Document start and stop time of placebo administration and the total volume administered (unblinded staff).
  - Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after placebo administration (blinded staff). Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.
  - Adverse event and serious adverse event assessment (starting at beginning of placebo injection) (blinded staff).

6.3.2 Day 7 Visit

All participants will return to the clinic for study drug dosing on Day 7($\pm$2). Prior to the administration of the study drug, the participant will be evaluated clinically to assess the development of clinically significant conditions that may contraindicate dosing.

Note: To avoid unblinding on the dose administration worksheet, if a participant is under 50 kg, the volume of FCM or placebo administered should be calculated based on the participant's weight, e.g. a 45 kg participant will receive a 13.5 mL dose of FCM or placebo.

Group A participants the following will be performed:

- Verify amount of single FCM dose (15 mg/kg up to a maximum dose of 750 mg) (unblinded staff)
- Pre-administration, obtain heart rate, blood pressure, and body temperature (blinded staff)

- Administer FCM as a slow IV injection at the rate of approximately 2 mL /minute taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff).
- Document start and stop time of FCM administration and the total dose and volume administered (unblinded staff).
- Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after FCM administration (blinded staff). Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.
- Adverse event / serious adverse event assessment, including evaluation of potential endpoint events (see Section 10.2; blinded staff)
- Review concomitant medications

Group B participants the following will be performed:

- Pre-administration, obtain heart rate, blood pressure, and body temperature (blinded staff)
- Administer a 15 mL dose of placebo (normal saline) as a slow IV injection at the rate of approximately 2 mL /minute taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff).
    - Document start and stop time of placebo administration and the total volume administered (unblinded staff).
    - Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after placebo administration (blinded staff). Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.
    - Adverse event/serious adverse event assessment, including evaluation of potential endpoint events (see Section 10.2; blinded staff).
    - Review concomitant medications (blinded staff)

6.4 Follow-Up Phase

6.4.1 90 Day Follow-Up

Following the initial and all subsequent courses of study drug treatments each participant will be contacted in person or via telephone 90±14 days post the first treatment for that course (i.e. study Days 90±14, 270±14, 450±14, 630±14, 810±14, 990±14…EOS)

During these visits the following will be performed:

- Adverse event / serious adverse event assessment, including evaluation of potential clinical endpoint events (see Section 10.2). (blinded staff)

6.4.2 6 Month Laboratory Evaluation

Participants will receive an additional course of study medication every 180 (±7) days. Within 4 to 20 days prior to these scheduled dosing visits, all participants will return to the clinic to obtain central lab hematology, chemistry, and iron indices laboratory tests. 1,25 $(OH)_2$ Vitamin D, 25 (OH) Vitamin D and PTH for participants of the hypophosphatemia sub-study. (Blood to be collected by blinded staff)

6.4.3 Additional Study Drug Dosing (Every 6 Months)

All participants will be dosed every 6 months. At each 6-month interval, a course of 2 doses of study drug will be administered as described above for Day 0 and Day 7 (Section 6.3). For group A, FCM will be administered if Hgb < 13.5 g/dL (females) or <15.0 g/dL (males) and serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%; observe carefully that placebo (normal saline) will be administered to participants in the FCM group who do not meet the above criteria. All group B participants will receive placebo (normal saline).

6.4.3.1 6 Month Dosing Visit #1 (Days 180±7, 360±7, 540±7, 720±7, 900±7, 1,080±7…EOS)

On the first of the 2 dosing visits, the following will be performed by blinded study staff for all participants:

- Weight
- Urine or serum pregnancy test (women of childbearing potential only)
- Adverse event / serious adverse event assessment, including evaluation of potential endpoint events (see Section 10.2).
- Review concomitant medications
- Administer 6MWT per standardized procedure (at the 6 and 12 month visits).

Note: To avoid unblinding on the dose administration worksheet, if a participant is under 50 kg, the volume of FCM or placebo administered should be calculated based on the participant's weight, e.g. a 45 kg participant will receive a 13.5 mL dose of FCM or placebo.

For Group A participants the following will be performed:

- Verify if participant will receive FCM or placebo, based on the following criteria from recent labs (within 20 days). Participants will receive FCM if the Hgb <13.5 g/dL (females) or <15.0 g/dL (males) and serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%. If the participant does not meet these criteria, placebo (normal saline) will be administered. (unblinded staff)
- As appropriate based on criteria above, verify amount of single FCM dose (15 mg/kg up to a maximum dose of 750 mg) or placebo (15 mL). (unblinded staff)
- Pre-administration, obtain heart rate, blood pressure, and body temperature. (blinded staff)
- Administer FCM or placebo as a slow IV injection at the rate of approximately 2 mL /minute. Appropriate measures must be taken to ensure the participant and all blinded

staff members remain blinded to the treatment being administered (unblinded staff)

- Document start and stop time of IV administration, and the total dose and volume administered (unblinded staff)
- Post-administration of FCM, obtain heart rate and blood pressure immediately after and 30 minutes after FCM administration (blinded staff). Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.

For Group B participants the following will be performed:

- Pre-administration, obtain heart rate, blood pressure and body temperature. (blinded staff)
- Administer a 15 mL dose of placebo (normal saline) as a slow IV injection, at the rate of approximately 2 mL /minute. Taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff)
    - Document start and stop time of placebo administration and the total volume administered. (unblinded staff)
    - Post-administration of placebo, obtain heart rate and blood pressure immediately after and 30 minutes after placebo administration (blinded staff). Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.

6.4.3.2 Six Month Dosing Visit #2 (Days 187±7, 367±7, 547±7, 727±7, 907±7, 1,087±7…EOS)

The second of the 2 dosing visits should occur at Day 7 (±2) after the first, with the following performed for all participants:

- Adverse event / serious adverse event assessment, including evaluation of potential endpoint events (see Section 10.2). (blinded staff), and review of concomitant medications (blinded staff).

Note: To avoid unblinding on the dose administration worksheet, if a participant is under 50 kg, the volume of FCM or placebo administered should be calculated based on the participant's weight, e.g. a 45 kg participant will receive a 13.5 mL dose of FCM or placebo.

For Group A participants the following will be performed:

- Verify amount of single FCM dose (15 mg/kg up to a maximum dose of 750 mg) or placebo (15 mL). Note: participant should receive the same product (FCM or placebo) as received at the first dose of this course of treatment. (unblinded staff)
- Pre-administration, obtain heart rate, blood pressure, and body temperature. (blinded staff)
- Administer FCM or placebo as a slow IV injection at the rate of approximately 2 mL

/minute. Taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff).

- Document start and stop time of IV administration and the total dose and volume administered. (unblinded staff)
- Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after FCM administration. (blinded staff). Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.

For Group B participants the following will be performed:

- Pre-administration, obtain heart rate, blood pressure, and body temperature (blinded staff).
- Administer a 15 mL dose of placebo (normal saline) as a slow IV injection, at the rate of approximately 2 mL /minute. Taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff)
  - Document start and stop time of placebo administration and the total volume administered. (unblinded staff).
  - Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after placebo administration. (blinded staff). Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.

6.5 End of Study Visits

End of study visits for all participants will be scheduled once the last participant has reached 12 months on study and at least 771 participants have experienced an event of cardiovascular death or hospitalization for heart failure. The participants should return to the clinic and the following will be performed by blinded study staff:

- Targeted physical exam
- Vital signs including BP and heart rate
- Blood samples for central lab hematology, chemistries, iron indices and NT-proBNP.
- Urine or serum pregnancy test (women of childbearing potential only)
- Review of concomitant medications
- Adverse event / serious adverse event assessment, including evaluation of potential endpoint events (see Section 10.2).

6.6 Laboratory Assessments

Serum samples for laboratory analyses must be obtained at all appropriate visits. The method of analysis of screening laboratory values will be by a central clinical laboratory. All visit laboratory samples will be analyzed by a central clinical laboratory. All laboratory testing will be provided to the investigator or his/her

medically qualified designee for review and assessment. Post dose iron indices and serum phosphorus results will be provided to the designated unblinded investigator for assessment. The laboratory assessments will be determined as listed in Section 3.3:

Hematology:	Hgb, Hct, RBC, WBC, MCV, MCH, MCHC, RDW, platelets, differential count, and reticulocyte count
Chemistry:	Sodium, potassium, chloride, BUN, creatinine, albumin, alkaline phosphatase, total bilirubin, GGT, AST, ALT, LDH, calcium, phosphorus, glucose, bicarbonate, and magnesium
Iron indices:	Serum iron, serum ferritin, total iron binding capacity (TIBC), and percentage serum transferrin saturation (TSAT)
Other:	1,25 $(OH)_2$ Vitamin D, 25 (OH) Vitamin D and PTH, and NT-proBNP

7.0 ASSESSMENT OF SAFETY

7.1 Adverse Events

Any untoward medical event experienced by a participant during the course of this clinical trial, whether or not it is related to the investigational product, at any dose, is considered an adverse event (AE).

For any laboratory abnormality, the investigator, or his/her medically qualified designee, will make a judgment as to its clinical significance. If the laboratory value is outside the normal limits and is felt to represent a clinically significant worsening from the baseline value, it should be considered an adverse event. If the laboratory value is outside the normal range, but not an adverse event, the investigator should comment on the findings (i.e. “not clinically significant” or “unchanged from baseline”) in the source documentation [laboratory report].

Table 7.1.1 Grading of Adverse Event Severity

Grade	Adjective	Description
1	Mild	Does not interfere with the participant’s usual function
2	Moderate	Interferes to some extent with participant's usual function
3	Severe	Interferes significantly with participant's usual function
4	Life-threatening	Results in a threat to life or in an incapacitating disability
5	Death	Results in Death

Timing: Adverse events and serious adverse events will be reported, as described below in Section 7.2, from the time of randomization through the end of study. Adverse events for participants randomized and who terminate early will be reported for 30 days after the last treatment.

Timing: Adverse events and serious adverse events will be reported, as described below in Section 7.2, from the time of randomization through the end of study. Adverse events for participants randomized and who terminate the study early or permanently discontinue study drug (Section 4.5) will be reported for 30 days after the last treatment. All reported SAEs should be followed until no longer serious or return to baseline grade.

Relationship (Causality): The Investigator will be asked to document his/her opinion of the relationship of the event to the study drug* as follows:

- NONE There is *no* evidence of any causal relationship.
- UNLIKELY There is *little* evidence to suggest there is a causal relationship. There is *another reasonable explanation* for the event (e.g., the participant's clinical condition, other concomitant treatments).
- POSSIBLE There is *some* evidence to suggest a causal relationship (i.e. there is a reasonable possibility that the adverse experience may have been caused by the agent). However, the influence of *other factors may have contributed* to the event (e.g., the participant's clinical condition, other concomitant events).
- PROBABLE There *is evidence* to suggest a causal relationship, and the influence of other factors is *unlikely*.

* For the purposes of this trial, "study drug" is defined as:

FCM

OR

Placebo

7.2 Reporting of Adverse Events

For the purposes of this study, any AE that does not meet the protocol definition of a serious AE is considered non-serious.

All SAEs and only AEs leading to study drug discontinuation will be collected in this study. Non-serious AEs that do not lead to study drug discontinuation (Section 4.5) are not being collected in this study.

Adverse experiences will be elicited by nonspecific questions such as "Have you noticed any problems?" Participants will be encouraged to report adverse events at their onset.

Disease progression can be considered as a worsening of a patient's clinical condition attributable to the disease in the patient population for which the study medication is being studied. It may be an increase in the severity of the disease under study, and/or increases in the symptoms of the disease. These also include the events listed in Section 7.4, "Reporting of Events that May Require Adjudication."

The development of the following cardiovascular disease events will be recorded in the eCRF, however they should be considered as disease progression and will not be reported as an AE/SAE during the study unless determined to be clinical endpoints.

1. Supraventricular arrhythmia (e.g., atrial fibrillation) requiring urgent/emergent intervention
2. Ventricular arrhythmia (e.g., ventricular tachycardia or fibrillation) requiring urgent/emergent intervention including ICD shock
3. Renal failure requiring urgent/emergent intervention (e.g., initiation of dialysis)

These three events will be documented on a dedicated form in the eCRF and they will be reported to the DSMB. An analysis as well as summary data tables of these events will be provided in the safety section of the clinical study report which will also include a rationale for exclusion of these events from AE or SAE reporting. Data files containing information about the above events will be included in the Regulatory submission in addition to hyperlinks or other means to easily direct reviewers to the location of the data.

7.3 Serious Adverse Events

Definition: An adverse event is classified as SERIOUS if it meets any one of the following criteria:

- **Death**
- **Life-Threatening:** The participant was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the participant's death.
- **Hospitalization (initial or prolonged):** Required admission to the hospital or prolongation of a hospital stay except events which are components of the primary or secondary endpoints which will be adjudicated by the CEC Committee as noted above.
- **Disability:** Resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the participant's body function/structure, physical activities or quality of life.
- **Congenital Anomaly/Birth Defect.**
- **Important medical events:** Other medically important events that, in the opinion of the investigator, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above.

Suspected clinical endpoint events that may traditionally meet the definition of an SAE, will not be reported by the sites in this trial as an SAE, but will be reported as a suspected clinical endpoint. Those events will therefore not be reported to the sponsor's Drug Safety Surveillance department.

Certain events of interest (supraventricular arrhythmia, ventricular arrhythmia, and renal failure) that are related to heart failure (serious and non-serious) will be listed on the eCRF and not be reported by the site as an SAE.

These events will be monitored by the Data Safety Monitoring Board to ensure participant safety.

Additionally suspected clinical events that are reviewed by the CEC but do not meet the criteria of an endpoint event will then be reviewed by the safety surveillance team for possible unreported SAEs.

Reporting: **Any SAE as defined by this protocol, starting with the time of randomization, that is to be reported (as outlined in the section above) must be reported immediately (by the end of the next business day) to American Regent, Inc. This occurs through entry into the eCRF by the local investigator/coordinator and completing the SAE module. In the event that the eCRF module is not available and paper forms have not been provided for use, the investigator will contact the Study Safety Monitor at:**

American Regent, Inc.

[redacted]

[redacted]

The local investigator is responsible for reporting SAEs to their local IRB/ Ethics Committee based on local reporting guidelines (which may be different than those specified in this protocol). The responsible investigator should institute appropriate diagnostic and therapeutic measures and keep the participant under observation for as long as is medically indicated.

7.4 Reporting of Suspected Study Endpoint Events that May Require Adjudication

The following events, which are the components of the primary or secondary endpoints will be adjudicated by the Clinical Events Classification (CEC) Committee of the Duke Clinical Research Institute (DCRI) for both FCM and Placebo and will not require reporting to the sponsor as an SAE:

- Cardiovascular Death including:
  - Death due to Heart Failure
  - Death due to Acute Myocardial Infarction
  - Sudden Cardiac Death

    - Death due to Stroke
    - Death due to other cardiovascular causes
- Hospitalization for heart failure
- Non-Cardiovascular death
- Hospitalization for myocardial infarction
- Hospitalization for stroke
- Other Cardiovascular hospitalizations
- Urgent heart failure visits

Therefore, any event that may possibly constitute one of these endpoints will be evaluated by the CEC Committee by a procedure described in separate documentation. A description of the CEC Committee and the definitions of the above clinical endpoints may be found in Section 10.2.

8.0 STATISTICAL METHODS

All statistical tests will be two-tailed. Type I error of 0.05 is assumed unless otherwise specified. No adjustments for multiple testing will be made. Complete details for the summary and statistical analysis of data to be collected will be documented in a Statistical Analysis Plan (SAP), which will be finalized prior to unlocking of the study base. The important elements of the planned methods are provided below.

8.1 Stratification/Randomization

Participants who meet the inclusion/exclusion criteria will be randomized in a 1:1 ratio on Day 0 to FCM or Placebo with stratification by region.

8.2 Analysis Populations

The Intent-To-Treat (ITT) Population will consist of all participants randomized to a treatment group in the study regardless of compliance with the study medication. For all analyzed using the ITT population, participants will be analyzed as randomized. This is the primary population of all efficacy analyses.

The Per-Protocol Population is a subset of the ITT population excluding participants who complied with the randomized treatment for less than 50% of the follow-up. In cases of medication error, treatment assignments in the per-protocol analysis will be analyzed according to the actual treatment received.

8.3 Disposition and Baseline Characteristics

The number and percent of participants who are randomized, treated with randomized therapy, prematurely discontinue, and complete the study will be summarized. The number and percent of participants will be summarized for each reason for premature discontinuation.

Categorical baseline characteristics (e.g., sex and race) will be summarized with the number and percent of participants in each treatment group with the characteristic. Quantitative characteristics (e.g., age and weight) will be summarized with the mean, median, standard deviation, minimum value, and maximum value. Baseline characteristics will be summarized for the safety and ITT populations.

8.4 Endpoints and Definitions

8.4.1 Primary Outcome

The primary outcome follows an ordinal scale of clinical severity comprised of 1) death, 2) number of hospitalizations for heart failure (as defined in Section 10.2) evaluated at one year; or 3) change in 6MWT evaluated at 6 months.

8.5 Secondary Outcomes

The following secondary outcomes will be evaluated in the hierarchy listed below.

1. Time to first event of the composite of cardiovascular death or heart failure hospitalization. The composite endpoint will be composed of adjudicated occurrence (as defined in Section 10.2) of one of the following:

    a. Cardiovascular Death
        i. Death due to Heart Failure
        ii. Death due to Acute Myocardial Infarction
        iii. Sudden Cardiac Death
        iv. Death due to Stroke
        v. Death due to other Cardiovascular Causes
    b. Hospitalization for Worsening Heart Failure

2. Mean change in 6MWT from baseline to 12 months
3. Time to first event of the composite of cardiovascular death or intervention for worsening heart failure (hospitalization or urgent heart failure visits)
4. Time to first event of the composite of cardiovascular death and cardiovascular hospitalizations
5. Time to cardiovascular death

Additional events to be adjudicated for analysis of the secondary endpoints include:

a) Non-cardiovascular death
b) Hospitalization for myocardial infarction
c) Hospitalization for stroke
d) Other cardiovascular hospitalizations
e) Urgent heart failure visits

A Clinical Events Classification (CEC) Committee at DCRI will review all potential events comprising all endpoints, and make the final determination whether an endpoint event has occurred for each participant (See Section 10.2).

8.6 Primary Comparison

Each participant from the treatment arm gets ranked/compared with each participant from the control arm based on the 12-month experience for Death and Hospitalizations for heart failure and 6 month results for change in 6MWT to determine treatment response per the following hierarchy:

1. **Death**
   If both die, the one who survives longer is better off;
   If one dies and one does not, the one that survives is better off;
   If neither dies, examine hospitalizations for heart failure.

2. **Hospitalizations for heart failure**
   The one with fewer hospitalizations is better off;

   If neither has been hospitalized for heart failure or the number heart failure hospitalizations is equal, compare change in 6MWT.

3. **Change in 6MWT**
   The one with higher change in 6MWT is better off;

Statistical Test

The main comparison will be conducted using the Wilcoxon-Mann-Whitney test. The null hypothesis being tested is that a randomly chosen participant in the treatment arm is equally likely to be ranked better or worse than a randomly chosen participant in the control group. The two-sided alternative is that the participant is not equally likely to be ranked better or worse. In addition to performing the test we will estimate the probability that a participant in the treatment arm has a better rank than a participant in the control arm and its corresponding confidence interval.

The above comparison of participants in the treatment versus control arms is equivalent to ranking all participants according to their experience. At one end of the ranking are participants with the best experience - those alive and not hospitalized for worsening heart failure ordered according to their improvement in 6MWT; at the opposite end are those who die ordered according to their survival time. Those participants alive but hospitalized are in the middle, ordered according to their number of hospitalizations for worsening heart failure and then by their change in 6MWT. The non-parametric Wilcoxon-Mann-Whitney test sums the ranks of those in the treatment arm and compares them with the sum of ranks in the control arm.

In all analyses the number of hospitalizations (and the number of days in the hospital in the sensitivity analysis described below) will be adjusted for the time on follow-up. This

adjustment applies only to individuals who are alive at the end of follow-up (the comparison in those who die will be resolved based on time to death) and will be accomplished by dividing the observed number by time at risk in years. For individuals who complete the pre-specified 12 months of follow-up, time at risk equals 1. For all others, it is equal to the fraction of 12 months that the person remained in the study.

8.7 Secondary Comparisons

8.7.1 Top Secondary Comparison: Time to first event of cardiovascular death or hospitalization of heart failure

This analysis will compare time to first occurrence of cardiovascular death or hospitalization for heart failure. The Cox proportional hazards model will be employed to conduct this comparison. The test will be two-tailed and will be performed at an overall α of 0.05. This analysis will be performed by the ITT principle based on randomized treatment assignment and we expect adequate power to detect a pre-specified relative risk reduction of 20%.

Sensitivity Analysis

In a sensitivity analysis we will add another layer to the hierarchy described above – in individuals who have been hospitalized for heart failure during follow-up, ties in the numbers of hospitalizations will be resolved based on the total number of days in the hospital during follow-up, before proceeding to comparison of differences in the 6MWT.

8.7.2 Change in 6 Minute Walk Test

Mean change in 6MWT distance from baseline to 12 months will be compared using linear regression adjusting for baseline value of 6MWT.

8.7.3 Secondary Outcomes based on time to first event

The time to each of the remaining secondary outcomes (Incidence of cardiovascular deaths and cardiovascular hospitalizations, Incidence of cardiovascular death or intervention for worsening heart failure (hospitalization or urgent heart failure visits) and Incidence of cardiovascular deaths) will be compared using the Cox proportional hazards model.

8.8 Sample Size and Statistical Power

The study design allows for sufficient power for both the primary and top secondary outcomes.

Numerical simulations based on multivariate normal vectors were conducted to estimate power for the primary treatment comparison based on the following assumptions about events rates described in Table 8.8.1.

Table 8.8.1. Assumptions About Event Rates for Primary Outcome

Ranked tier at 12-month endpoint (6 month for 6 MWT)	Control	Treatment
Death total	8%	6.8%
Death without hospitalization	4%	3.4%
Death with hospitalization	4%	3.4%
Hospitalizations in survivors		
1	6%	4.8%
2	3%	2.4%
3 or more	1%	0.8%
Change in 6 Minute Walk Test	Mean = 0 SD = 90	Mean = 18 SD = 90

With 3014 patients (1507 per arm) and 2.5% annual loss to follow-up for clinical outcomes and 15% of individuals with missing 6MWT at 6 months (unable to perform or lost to follow-up), projected simulations estimate 90% power at an overall two-sided significance level of 0.01, accounting for one interim analysis as described in section 8.10.

For the top secondary composite, an assumed event rate of 0.0128 per month in the control arm which represents conservative 75% discounting of the event rate obtained by the FCM meta-analysis [Anker 2015]. The anticipated hazard ratio was set at 0.80 (20% reduction). Uniform enrollment is assumed over the period of 30 months, with an anticipated minimum follow-up of 12 months (required minimum of 6 months), anticipated maximum follow-up of 42 months (no required maximum), and monthly loss to follow-up of 0.0021 (2.5% annualized). With these assumptions, 1500 per study arm (3000 total) provides 90% power to reject the null hypothesis of no difference between treatment arms when tested at an overall two-sided level of significance α =0.05, accounting for one interim analysis as described in section 8.10. This results in a total of 771 events necessary to achieve the desired power. Thus, the trial has the potential opportunity to be stopped at a point where the projected number of events reaches 771, but no earlier than the last participant reaching 12 months of follow-up.

The primary and top secondary outcome will be tested sequentially, and thus, no multiplicity adjustment is necessary.

8.9 Handling of Missing Data

Every effort will be made to limit the number of missing data points. The trial will be conducted in jurisdiction which will allow ascertainment of vital status even in individuals who discontinue the study. Participants who discontinue taking study drug should be encouraged to continue participation in the trial so that endpoint data can be collected.

Furthermore, consent will be obtained to examine hospital records where feasible. Partnership with transportation companies will be fostered to decrease the burden of travel to clinic visit and increase the likelihood of the final study visit taking place.

The prospective plan for the handling of missing data is as follows:

The primary analysis will rely on a multiple imputation model, with Markov chain Monte Carlo algorithm based on the totality of observed data. One exception to this rule will be individuals unable to perform the 6MWT test at 6 months will have their value imputed as the worst observed change in 6MWT.

Two supporting analyses will be undertaken. The first one will use multiple imputation for clinical outcomes, but will impute the worst observed change in 6MWT to all individuals who do not have this measurement, regardless of the reason.

The second series of analyses will perform tipping point assessments to determine the sensitivity of the observed result to the missing data. Given the multi-dimensional nature of outcomes, tipping point analyses will be performed separately for each outcome: mortality, hospitalization for heart failure and 6MWT.

8.10 Stopping Rules and Interim Analysis

A Data and Safety Monitoring Committee (DSMB), with statistical support from DCRI will review safety data, including a tally of the composite outcome events at least every 6 months (See Section 10.3). The DSMB can recommend stopping the study for safety concern at any point. In addition, one interim analysis is planned to determine if an early stopping for an overwhelming efficacy should be recommended. This analysis will be conducted after 2250 (75%) participants have been enrolled. Significance level will be set at 0.0001 for this analysis, resulting in an adjusted significance level for the final analysis of 0.0099 for the primary endpoint and 0.0499 for the first secondary endpoint, preserving the overall significance at 0.01 and 0.05, respectively. Conditional power will be estimated based on data accrued to date and presented to the DSMB. The DSMB may recommend that the study continues as planned, discontinue the study or that the trial be continued with recommended changes to the protocol. The Executive Steering Committee will determine if an increase in sample size is warranted in order that at least 771 participants will experience an event of cardiovascular death or hospitalization for heart failure.

9.0 ADMINISTRATIVE CONSIDERATIONS

9.1 Retention and Availability of Records

Investigators are required to maintain all study documentation, including a copy of the CRFs, Informed Consent documents, and adequate records for the receipt and disposition of study medications, for a period of two years following a supplemental application for the drug for the indication being investigated, or until two years after the drug investigational program is discontinued.

The Investigator must make study data accessible to the monitor, Sponsors, or other authorized representatives of the Sponsor and Regulatory Agency (i.e., FDA inspectors.) A case history for each participant must be maintained, that includes the signed Informed Consent form and copies of all study documentation related to that participant. The investigator must ensure the availability of source documents including the electronic health record, if applicable, from which the information on the eCRF was derived.

9.2 Investigator Responsibilities

By signing the Form FDA 1572 the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor, except when necessary to protect the safety, rights or welfare of participants.
2. Personally conduct or supervise the study (or investigation).
3. Inform any participants that the drug is being used for investigational purposes.
4. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet Federal guidelines, as stated in 21 CFR, parts 50 and 56.
5. Report to the Sponsor any adverse events that occur in the course of the study, in accordance with 21 CFR 312.64.
6. Have read and understood the Investigator's Brochure, including potential risks and side effects of the drug.
7. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
8. Maintain adequate and accurate records, in accordance with 21 CFR 312.62 and to make those records available for inspection with the Sponsor, their designated representative, the FDA or any agency authorized by law.
9. Ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for initial and continuing review and approval of the clinical study.
10. Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to participants or others (including amendments and IND safety reports).
11. Not make any changes in the research study without approval, except when necessary to eliminate hazards to the participant/participants.
12. To comply with all other requirements regarding the obligations of the clinical investigators and all other pertinent requirements listed in 21 CFR Part 312.

9.3 Financial Disclosure

All principal investigators and co-investigators will be required to complete FDA-required financial forms provided by American Regent, Inc. All signed financial disclosure forms must be submitted to the Sponsor prior to the site enrolling participants into the study.

9.4 Advertisement for Participant Recruitment

All advertisement for participant recruitment must be reviewed and approved by the Sponsor and the site's IRB prior to implementation. Advertisement may include but is not limited to: newspaper, fliers, radio, television, and the use of social media by a central advertising campaign. Any compensation to the participant included in the advertisement must be identical to the compensation stated in the IRB-approved informed consent.

9.5 Documents Required for Study Initiation

Prior to study initiation, the investigator must provide Luitpold Pharmaceuticals Inc. or its designee with the following documentation:

- Curriculum Vitae and medical license for Principal Investigators and co-investigators.
- Form FDA 1572
- Financial disclosure form
- IRB approval of protocol and informed consent
- Copy of IRB approved informed consent
- IRB membership list or assurance number
- Protocol signature page
- IRB approval of any advertising for participant recruitment [if applicable]
- Copy of advertising [if applicable]
- IRB approval of translation of informed consent [if applicable]

9.6 Quality Control and Quality Assurance

9.6.1 Investigator Selection Criteria

Each investigator participating in this study will meet the following criteria:

- Accessible, interested, and available support staff.
- Availability of adequate facilities to support study requirements.
- Availability of physician emergency response at all times.
- Adequate time to conduct study.
- Adequate training and experience of personnel to conduct study.
- Ability to recruit enough participants to conduct study.

Prior to investigator selection, each site will be evaluated to ensure they meet the criteria noted above.

American Regent, Inc. and/or their designee will insure that no investigator is on FDA’s Debarment List or Disqualified Investigator List.

9.6.2 Clinical Monitoring

This study will be monitored by the Sponsor (or its designee) in accordance with FDA and International Conference on Harmonisation Good Clinical Practices (GCPs), 21CFR Part 312. As part of a concerted effort to follow the study in a detailed and orderly manner, in accordance with established principles of GCP and applicable regulations, a Monitor will visit the site according to the monitoring plan and will maintain telephone and written communication throughout the duration of the study.

Periodic monitoring visits will be made to the site during the clinical study to assure that the Investigator obligations are fulfilled, and all applicable regulations and guidelines established by the protocol are being followed.

These visits will assure that the facility is still acceptable, the protocol and investigational plan are being followed, the IRB/EC has been notified of approved protocol changes as required, complete study records are being maintained, appropriate and timely reports have been made to the sponsor or its representative and the IRB/EC, study drug inventory is controlled, and the Investigator is carrying out all agreed-upon activities.

In accordance with the FDA *Guidance for Industry: Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring,* a combination of on-site and centralized monitoring practices will be implemented in order to ensure participant protection, as well as quality and integrity of the clinical trial data while promoting efficiency. While the majority of monitoring will be conducted centrally, on-site monitoring will be performed based on the findings of previous on-site monitoring visits and centralized monitoring. During on-site monitoring, a percentage of the data will be compared among the eCRF (i.e. source document review, source document verification) and each participant's source documentation, and data discrepancies will be queried. See the trial specific risk based monitoring plan for additional details.

9.6.3 Quality Assurance Audit

For the purpose of data validation, the principal investigators will permit a member of the quality assurance unit of American Regent, Inc. or its designee to inspect the source data and compare them with the eCRFs. Pre-study audits, interim audits and post-study audits may be performed and may also include review of facilities, equipment, pertinent site documentation, and personnel qualifications. Notification of these audits will be sent to investigators in advance.

9.7 Ethics

9.7.1 Ethical and Legal Issues

This study will be performed in accordance with the U.S. Code of Federal Regulations on Protection of Human Participants (21 CFR 50), IRB regulations (21 CFR 56), the most recent revision of the Declaration of Helsinki, all applicable local and state regulations, 21 CFR Part 312, and applicable ICH guidelines.

9.7.2 Institutional Review Board

The Protocol and the Informed Consent must be approved by an appropriate Institutional Review Board (IRB) before the study is initiated. Documentation of this approval must be provided to the Sponsor or designee. The IRB must comply with current U.S. Regulations (21 CFR 56) for the protection of Human Subjects in Research. Investigators are responsible for the following:

- Obtain IRB approval of the protocol, Informed Consent, and any advertisements to recruit participants; obtain IRB approval for any protocol amendments and Informed Consent revisions before implementing the changes.
- Provide the IRB with any information it requests before or during the study.
- Submit progress reports and a final report to the IRB, as required, during the conduct of the study; request re-review and approval of the study as needed; provide copies of all IRB re-approvals and relevant communication with the Sponsor.
- Notify the IRB of all serious adverse events that occur or are reported to you by the Sponsor as required by the IRB.

9.7.3 Informed Consent

Each investigational site must provide the Sponsor (or designee) with a copy of the Informed Consent approved by the site's IRB. The Clinical Monitor will assure that each Informed Consent meets the requirements of Parts 50.20 and 50.25 of Title 21 of the CFR, which outlines the basic elements of informed consent and ICH guidelines prior to its use.

Informed consent must be obtained from each participant prior to enrollment. The informed consent will be provided to the participant in their native language. The Informed Consent must be signed and dated by each participant before entering the study, and prior to the performance of any study-specific procedures. The original signed consent form will be retained in the participant's study records, and a copy will be provided to the participant. Translations of the informed consent must be certified by a qualified translator and their use must be documented.

The Informed Consent documents the information the Investigator provides to the participant and the participant's agreement to participate. The Investigator will fully explain the nature of the study, along with the purpose, methods, anticipated benefits, potential hazards, and discomfort that participation might entail.

9.7.4 Good Clinical Practice

The conduct of the study will conform with the recommendations for clinical studies in humans as set out in the most current revision of the “Declaration of Helsinki”, the local legal requirements and the guidelines on “Good Clinical Practice”, [21 CFR Part 312 and ICH guidelines].

9.8 Data Handling and Record Keeping

9.8.1 Case Report Form

The eCRFs will be completed for each participant on this study. The participants in this study will be identified only by a participant number and date of birth on these forms.

The eCRF used will be 21 CFR 11 compliant. The system used for data collection (eCRF) will meet all applicable regulatory requirements for recordkeeping and record retention as would be provided with a paper system. Security measures will be utilized to prevent unauthorized access to the data and to the computerized system. Changes made to data that are stored on electronic media will always require an audit trail, in accordance with 21 CFR 11.10(e).

The eCRFs must be reviewed and verified for accuracy by the Principal Investigator. An electronic copy of the eCRF will remain at the site at the completion of the study.

9.8.2 Confidentiality

All unpublished information given to the investigator or institution dealing with this study, study drug or the conduct, financial agreements, or methodologies used in this protocol, as well as information obtained during the course of the study, remains confidential and proprietary to the Sponsor [“Proprietary Information”]. The Investigator shall not disclose any such Proprietary Information to any third party without prior written consent from the sponsor [See also Section 9.9 Publication Policy]. For purposes of this Section, “Investigator” includes, but is not limited to the Principal Investigator and/or his/her agents, designees, sub-investigators or other individuals involved in the running, administration, collection or evaluation of participants or data for this study.

All pharmaceutical formulations supplied for the purpose of the trial shall remain the sole property of American Regent, Inc. They will be used for the purposes specified in the protocol. Any unused medication will be returned to the sponsor at the conclusion of the study.

No patent application based on the results of this study should be made by the investigator and all such rights assigned to American Regent, Inc., and no assistance should be given to any third party to make such an application without the written authorization of American Regent, Inc.

9.8.3 Termination of the Study

The study may be terminated if the DSMB, Sponsor, or Steering Committee discovers conditions arising during the course of the study, which indicate that the clinical investigation should be halted. The study may be terminated after appropriate consultation and discussion.

Conditions that may warrant study termination include, but are not limited to, the discovery of a significant, unexpected and unacceptable risk to the participants, failure of the

investigator to enroll participants at an acceptable rate, insufficient adherence to the protocol requirements, completion of study objectives, or at the discretion of the sponsor.

9.8.4 Protocol Revisions

Changes in any portion of this protocol that affect participant safety or welfare or which alter the scientific validity of the study must be documented in the form of an amendment. This change must be signed by the appropriate Luitpold personnel and the investigator and be approved by the site's IRB, before the revision may be implemented. The protocol revision will be submitted to the FDA.

9.8.5 Protocol Administrative Changes

Clarification or interpretation of the study protocol or changes in the methods of statistical analysis may be documented in the form of a numbered memo or other applicable document (charter, plan, etc.). Numbered memos do not typically require the investigator's signature or IRB approval.

9.9 Publication Policy

All information resulting from this study is the Proprietary Information of American Regent, Inc., as per the Confidentiality Section of this protocol. The Steering Committee will be responsible for the manuscript describing the main study results, and oversee publications requiring trial data. A separate publication charter will govern the process of publications.

American Regent, Inc., and the Steering Committee shall have final and sole control over the content of any publication. The Principal Investigator and any sub-investigators may make presentations on the study, or may publish results of the study at their site, but only after the results of the study have been published, or with the prior approval of American Regent, Inc.

The Investigator will provide to the Sponsor any announcement, publication, or presentation of data from this study for the Sponsor's review and comments at least 10 days in advance of such disclosure. Sponsor may, at its sole discretion, require the removal of any proprietary information from the disclosure. The Investigator agrees to provide the Sponsor, at the Sponsor's discretion, with any byline credit in any publication proposed by the Investigator. This is in order to enable American Regent, Inc., to make constructive comments about the manuscript or text and to give the opportunity of assessing whether patent protection should be sought by Luitpold on any results or ideas connected with the study.

10.0 GOVERNANCE COMMITTEES

10.1 Steering Committee (SC)

The SC will be responsible for oversight of the study. The SC chair will be Dr. Adrian Hernandez of DCRI. The SC will consist of 6-12 members including the chair, primarily

from academic institutions, in addition to representation of the Sponsor. The SC will consist of experts in heart failure as well as cardiovascular outcomes trials.

The key functions of the SC will be to:

1. Review and approve the main protocol, amendments, and the Statistical Analysis Plan.
2. Determine the time to terminate the study based on recommendations from the DSMB and other available information.
3. Review and approve any substudies.
4. Draft the manuscript describing the main study results and oversee all publications requiring trial data
5. Participate where appropriate in scientific meetings providing updates of study progress.
6. Oversee trial subcommittees including the Clinical Endpoint Committee and the Data Safety Monitoring Board
7. Assume the role of the publications committee and review, authorize and prioritize proposals for publications which require trial or substudy data samples and assign writing groups

10.2 Adjudication by the Clinical Endpoint Classification (CEC) Committee

A Clinical Event Committee (CEC) will be created for this trial to review and adjudicate each suspected endpoint event while blinded to treatment in this study. The CEC for this trial will consist of cardiologists, neurologists, and physicians with clinical expertise from DCRI or other academic institutions. The CEC Chair will lead the development of the definitions of endpoints, instructions for interpretation, and provide ongoing oversight to the CEC members for this trial to ensure that events are adjudicated in consistent fashion over time. The CEC members, as well as those overseeing the CEC, will not be investigators in the study, or be otherwise directly associated with the sponsor, and will remain blinded to treatment throughout the study and the adjudication process. The CEC and the adjudication process will be described in detail in a separate CEC charter.

Adjudicated Endpoints

10.2.1 Death

All deaths will be categorized as **Cardiovascular or non-Cardiovascular** based on the definitions below. In addition, all deaths will further be sub-typed based on the specific cardiovascular categories defined below. Non-cardiovascular deaths will not be further adjudicated.

The cause of death will be determined by the principal condition that caused the death, not the immediate mode of death. For example, if a participant is hospitalized and undergoing treatment for worsening heart failure dies of ventricular tachycardia, this would be classified as a heart failure death. CEC physicians will utilize all available information provided, along with clinical expertise in their adjudication of cause of death.

10.2.1.1 Death Due to Cardiovascular Death

Cardiovascular death includes death resulting from an acute MI, sudden cardiac death, death due to heart failure, death due to stroke, and death due to other CV causes.

10.2.1.2 Death Due to Heart Failure

Death due to heart failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure regardless of heart failure etiology. Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

Deaths that occur during a heart failure hospitalization will generally be attributed to heart failure, even if there is another immediate mode of death (e.g, ventricular fibrillation). Deaths that occur in hospice or other similar palliative care setting for heart failure will generally be attributed to heart failure.

10.2.1.3 Death Due to Acute Myocardial Infarction

Death due to acute MI refers to a death by any CV mechanism (e.g. arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) ≤30 days after a MI related to the immediate consequences of the MI, such as progressive heart failure or recalcitrant arrhythmia. We note that there may be assessable mechanisms of CV death during this time period, but for simplicity, if the CV death occurs ≤30 days of the MI, it will be considered a death due to MI.

Acute MI should be verified to the extent possible by the diagnostic criteria outlined for CV hospitalization for acute MI, or by autopsy findings showing recent MI or recent coronary thrombosis.

Death resulting from a procedure to treat a MI, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from MI should also be considered death due to acute MI.

If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead ECG could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. Death resulting from a procedure to treat a myocardial infarction (e.g. PCI, CABG), or to treat a complication resulting from MI, should also be considered death due to acute MI.

10.2.1.4 Sudden Cardiac Death

Sudden Cardiac Death refers to death that occurs unexpectedly and not following an acute MI, and includes the following deaths:

- Death witnessed and occurring without new or worsening symptoms.
- Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute myocardial infarction.
- Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator (ICD) review)
- Death after unsuccessful resuscitation from cardiac arrest. (e.g., ICD unresponsive sudden cardiac death, pulseless electrical activity arrest)
- Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology
- Unwitnessed death in a participant seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information about the participant's clinical status preceding death should be provided, if available)

  General Considerations
  - Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a participant is seen alive ≤24 hours (or a reasonable period when otherwise clinically stable) of being found dead OR circumstances suggest sudden death, sudden cardiac death should be recorded

  Typical scenarios include:
  - Participant well the previous day but found dead in bed the next day
  - Participant found dead at home on the couch with the television on

  For participants who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (e.g., participant found dead in bed, but who had not been seen by family for several days).

  "Undetermined cause of death" will be considered as "CV death" for purpose of analysis.

10.2.1.5 Death Due to Stroke

Death due to Stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke in Section 10.2.2.3 (Hospitalization for Stroke).

10.2.1.6 Death Due to Other Cardiovascular Causes

Death due to Other Cardiovascular Causes refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolus, deep vein thrombosis, peripheral arterial disease, or aortic aneurysm).

10.2.1.7 Non-Cardiovascular Death

Non-cardiovascular death is defined as any death that is not thought to be CV in nature. Deaths from Non-CV causes will not be further subclassified.

10.2.1.8 Undetermined Cause of Death

Death not attributable to one of the above categories of CV death, or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g. the only information is "participant died"), or when there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classified as CV or non-CV, and the use of this category of death, therefore, should be discouraged and should apply to few participants.

All deaths adjudicated as "undetermined cause" will be presumed cardiovascular deaths, and as such, are part of the cardiovascular mortality endpoint.

10.2.2 Cardiovascular Hospitalizations

The participant's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date, if admission and discharge times are unavailable).

10.2.2.1 Hospitalization for Heart Failure

A Heart Failure hospitalization is defined as an event that meets **ALL** of the following criteria:

1) The participant is admitted to the hospital with a primary diagnosis of heart failure
2) The participant's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date, if admission and discharge times are unavailable).
3) The participant exhibits documented new or worsening symptoms due to heart failure on presentation, including at least ONE of the following:
    a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
    b. Decreased exercise tolerance
    c. Fatigue
    d. Other symptoms of worsened end-organ perfusion or volume overload (e.g., confusion, somnolence, edema, etc.)
4) The participant has objective evidence of new or worsening heart failure, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion), including:

    a. Physical examination findings considered to be due to heart failure, including new or worsened:
        i. Peripheral edema

ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
iii. Pulmonary rales, crackles, or crepitations
iv. Increased jugular venous pressure and/or hepatojugular reflux
v. S3 gallop
vi. Clinically significant or rapid weight gain thought to be related to fluid retention (usually more than 3-4 lbs in 3-4 days)

b. Laboratory evidence of new or worsening heart failure, if obtained within 24 hours of presentation, including:

i. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP >500 pg/mL or NT-proBNP >2,000 pg/mL). In patients with chronically-elevated natriuretic peptides, a significant (1.25X) increase should be noted above baseline

ii. Radiological evidence of pulmonary congestion

iii**. Non-invasive diagnostic evidence** of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' >15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI)

OR

iv. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mmHg, central venous pressure ≥12 mmHg, or a cardiac index <2.2 L/min/m2

Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

5) The participant receives initiation or intensification of treatment specifically for heart failure, including at least ONE of the following:
   a. Augmentation in oral diuretic therapy
   b. Intravenous diuretic, or vasoactive agent (e.g. positive inotrope, vasopressor or vasodilator)
   c. Mechanical or surgical intervention, including mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)

d. Mechanical fluid removal (e.g., ultrafiltration, Hemofiltration, dialysis)

10.2.2.2 Hospitalization for Myocardial Infarction

Acute MI will be adjudicated when a participant demonstrates at least one of the following biochemical indicators of myocardial necrosis:

• CK-MB greater than 2 x ULN or Troponin I or T greater than 2 x ULN, with a typical pattern of rise and fall consistent with MI

AND at least one of the two following criteria:

• Typical clinical presentation consistent with MI defined as typical cardiac ischemic type pain/discomfort or dyspnea felt to be due to ischemia

OR

• Typical ECG changes consisting of any of the following:
• New abnormal Q waves (or new R waves in lead V1-V2) in at least two consecutive leads
• Evolving, ischemic ST segment or T wave changes in at least two consecutive leads
• New LBBB

10.2.2.3 Hospitalization for Stroke

Stroke is defined as an acute episode of focal or global neurologic dysfunction caused by brain, spinal cord, or retinal vascular injury a result of hemorrhage or infarction. To be classified as a stroke, duration of a focal/global neurological deficit must have a duration >24 hours or imaging confirmation clearly documenting a new hemorrhage or infarct. Events may be classified as a stroke if symptoms were <24 hours due to either pharmacologic or non-pharmacologic interventions or the stroke resulted in death in <24 hours**.**

Classification:

Ischemic Stroke:

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Undetermined Stroke

Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, but with insufficient information to allow categorization as ischemic or hemorrhagic stroke.

10.2.2.4 Other Cardiovascular Hospitalizations

Urgent and unscheduled hospitalizations for other cardiovascular causes that do not meet the criteria for the specific events listed above will be classified as hospitalization for other cardiovascular causes. Examples would include, but are not limited to, hospitalization for cardiac chest pain that does not meet the criteria for MI, hospitalization for carotid events, hospitalization for deep vein thrombosis, hospitalization for arrhythmias, hospitalization for pulmonary embolism, etc. These hospitalizations will not be further sub-classified by the CEC.

10.2.3 Other Events: Urgent Heart Failure Visit

An urgent heart failure visit is defined as an event that meets all the following:

1) The participant has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of heart failure, but not meeting the criteria for a heart failure hospitalization
2) Signs and symptoms that constitute a heart failure hospitalization [i.e., 3) symptoms, 4) physical examination findings/laboratory evidence of new or worsening heart failure, as indicated above] must be met
3) The participant receives initiation or intensification of treatment specifically for heart failure, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient

10.3 Data and Safety Monitoring Board (DSMB)

The DSMB will be composed of approximately 5 senior academic individuals, including the DSMB Chair. The members will have high-level expertise in cardiology, hematology, clinical research, and statistics. A senior statistician assigned to the trial from the group performing data management services for this trial will oversee the provision of interim data reports for use by the DSMB. The data management group for this trial will transfer pre-agreed datasets to the statistician preparing data for DSMB. During the Open Session of the DSMB meetings, representatives of the SC or Luitpold representatives may present updates on the trial status or the safety profile of FCM, but will not be privy to discussions of the data conducted during the Closed Sessions and will not vote. Proceedings and minutes of the Closed Session will be held in strict confidence and will not be shared outside the DSMB while the trial is ongoing prior to database lock.

The DSMB will be responsible for the interests of the study participants, and to this end, will undertake regular reviews of the safety data. The DSMB will have access to an

agreed subset of the study data as listed in the DSMB charter (updated as necessary during the trial) throughout the study duration. In addition, the DSMB will evaluate interim analyses of the data every at least every six months (or on an ad hoc basis if needed) either by face-to-face meeting, or teleconference. The DSMB will determine if it believes the trial should be terminated early because clear evidence exists that either of the two groups has a treatment response that is substantially better than the other.

If the DSMB finds it necessary to recommend actions regarding interruption of the study, or changes to the protocol based on medical rationale that would make it unethical to continue the study in its present form, those recommendations will be forwarded to the SC. The details of the DSMB's functions and the early stopping rules will be delineated in a separate DSMB charter.

11.0 INVESTIGATOR'S ACKNOWLEDGEMENT

I have read this protocol and agree to conduct the study as outlined herein, complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR part 312 and all applicable local, state, and federal regulations and International Conference on Harmonisation guidelines.

_____

Investigator's signature

_____

Date

_____

Investigator's Name (Please print)

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13.0 Appendices

Appendix 1: Hypophosphatemia Sub-study

APPENDIX 1

AMERICAN REGENT, INCORPORATED

PROTOCOL NO. 1VIT15043

IND# 127910

A SUB-STUDY TO CHARACTERIZE SERUM PHOSPHORUS LEVELS OVER TIME WITH INTRAVENOUS FERRIC CARBOXYMALTOSE (FCM) VS. PLACEBO AS TREATMENT FOR HEART FAILURE WITH IRON DEFICIENCY

SPONSOR:

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For study-related questions, please contact:

[redacted]

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LIST OF ABBREVIATIONS

ALT	Alanine Aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Event
dL	Deciliter
e.g.	for example
FCM	Ferric Carboxymaltose
Fe	Iron
FGF-23	Fibroblast growth factor 23
g	Gram
GGT	Gamma-glutamyl transferase
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDA	Iron Deficiency Anemia
i.e.	that is
IV	Intravenous
Kg	Kilogram
L	Liter
LDH	Lactic dehydrogenase
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mL	Milliliter
N	Number
NCI	National Cancer Institute
PCS	Potentially clinically significant
SAP	Statistical Analysis Plan
SOC	System organ class
U.S.	United States
vs.	Versus
w/v	weight / volume

1. INTRODUCTION

Ferric Carboxymaltose (FCM) is a parenteral form of iron that can be used to treat iron deficiency (IDA) when oral iron is either ineffective or contraindicated [Lyseng-Williamson, 2009]. Several randomized controlled trials demonstrated the efficacy and safety of intravenous (IV) FCM for treating iron deficiency associated with chronic kidney disease, inflammatory bowel disease, heavy uterine bleeding, and during the postpartum period [Barish, 2012; Breymann, 2008; Evstatiev, 2011; Kulnigg, 2008; Qunibi, 2011; Seid, 2008; Van Wyck , 2007; Van Wyck, 2009;Charytan, 2012]. In these populations, several patients who received FCM developed transient and asymptomatic reductions in serum phosphate that typically appeared within 2 to 4 weeks of treatment and resolved spontaneously within 6 to 12 weeks [Van Wyck, 2009].

1.1. Pathophysiology

Phosphate is the most abundant intracellular anion and is essential for membrane structure, energy storage, and transport in all cells. Approximately 85% of the body's phosphorus is in bone as hydroxyapatite, while most of the remainder (15%) is present in soft tissue. Only 0.1 % of phosphorus is present in extracellular fluid and it is this fraction that is measured with a serum phosphorus level [Moe, 2008]. Phosphorus homeostasis is complex and is regulated by several hormones. Hypophosphatemia can occur in the presence of low, normal, or high total body phosphate. In the latter two instances, a shift from the extracellular pool into the intracellular compartment is a major contributory factor. Parathyroid hormone causes phosphate to be released from bone and inhibits renal reabsorption of phosphate, resulting in phosphaturia. Vitamin D aids in the intestinal absorption of phosphate. Thyroid hormone and growth hormone act to increase renal reabsorption of phosphate. Finally, a new class of phosphate-regulating factors, the so-called phosphatonins, including fibroblast growth factor 23 (FGF23), have been shown to be important in phosphate-wasting diseases, such as oncogenic osteomalacia, X-linked and autosomal dominant hypophosphatemic rickets, autosomal recessive hypophosphatemia, and tumoral calcinosis [Shaikh, 2008]. Additionally, FGF23 is up-regulated in patients with early-stage chronic kidney disease to prevent hyperphosphatemia [Takeda, 2011]. A link between IV iron application and increase in FGF23 has been proposed [Takeda, 2011; Schouten, 2009a].

Serum phosphorus concentration is determined by several factors. Dietary phosphorus intake, stage of growth and time of day contribute to the variability of fasting serum phosphorus concentrations. Optimal cellular function is dependent on maintenance of a normal serum phosphorus concentration. The most important determinant of serum phosphorus concentration is regulation of phosphorus reabsorption by the kidney. The majority of this reabsorption (80%) occurs in the proximal tubule and is mediated by an isoform of the Na-phosphate-cotransporter. Parathyroid hormone, via a variety of intracellular signaling cascades leads to Na-phosphate-IIa internalization and down-regulation, and is the main regulator of renal phosphate reabsorption.

Hypophosphatemia is observed in approximately 2% of hospitalized patients, and can be related to decreased intestinal absorption of phosphorus, re-distribution of phosphorus from the extracellular to the intracellular compartment, increased loss of phosphorus through the kidneys, or any combination of these processes. The most common manifestation of hypophosphatemia in hospitalized patients is secondary to re-distribution of phosphorus as a result of respiratory alkalosis [Amanzadeh, 2006]. Hypophosphatemia has been implicated as a cause of rhabdomyolysis, respiratory failure, hemolysis and left ventricular dysfunction. With the exception of ventilated patients, there is little evidence that moderate hypophosphatemia has significant clinical consequences in humans, and aggressive IV phosphate replacement is unnecessary.

The data on the incidence of hypophosphatemia (defined as <0.64 mmol/L) in outpatients is sparse, but has been reported as 0.9% [Betro, 1972].

1.2. Increased FGF23

Studies have shown that IV FCM, iron polymaltose and saccharated ferric oxide increase the levels of FGF23 post-infusion [Takeda, 2001; Schouten, 2009b; Wolf, 2013]. This hormone, besides the parathyroid hormone, is key for serum phosphate regulation. The phosphatonin FGF23 has been shown to decrease serum phosphate levels by reducing the number of Na-phosphate-cotransporters in the proximal tubule and by inhibiting the production of the active form of Vitamin D [Razzaque, 2007]. FGF23 is predominantly expressed in bone osteocytes [Liu, 2006]. Increased concentrations of circulating FGF23 are central to the pathogenesis of several hypophosphatemic diseases including autosomal-dominant, -recessive, and X-linked hypophosphatemic rickets, tumor-induced osteomalacia and selected cases of McCune-Albright syndrome [Imel, 2005; Yamamoto, 2005].

A study tested the association of IDA with cFGF23 (the C-terminal form of the protein) and iFGF23 (only the intact and hence active form) levels in 55 women with a history of heavy uterine bleeding, and assessed the longitudinal biochemical response over 35 days to equivalent doses of randomly assigned, IV elemental iron in the form of FCM or iron dextran [Wolf, 2013]. The IDA was associated with markedly elevated cFGF23 (807.8± 123.9 RU/mL) but normal iFGF23 (28.5± I. I pg/mL) levels at baseline. Within 24 hours of iron administration, cFGF23 levels decreased by approximately 80% in both groups. In contrast, iFGF23 transiently increased in the FCM group alone, and was followed by a transient, asymptomatic reduction in serum phosphate <2.0 mg P/dL in 10 women in the FCM group compared to none in the iron dextran group. Reduced serum phosphate was accompanied by increased urinary fractional excretion of phosphate, decreased calcitriol levels and increased parathyroid hormone levels. These finding suggest the IDA increases cFGF23 levels, and that certain iron preparations temporarily increase iFGF23 levels. It may therefore be concluded that IV iron lowers cFGF23 in humans by reducing FGF23 transcription as it does in mice, whereas carbohydrate moieties in certain iron preparations may simultaneously inhibit FGF23 degradation in osteocytes leading to transient increases in iFGF23 and reduced serum phosphate. Overall, it seems plausible

that an increase in iFGF23 with all the downstream effects may be induced by application of IV iron.

1.3. Inhibition of Vitamin D Activation

It has been described that IV iron might have an inhibitory effect on renal 25-(OH)-Vitamin D Iα-hydroxylase expression [Sato, 1997]. This in turn reduces the availability of 1,25-$(OH)_2$-Vitamin D_3, which leads to decreased absorption of phosphate from the gut and to decreased reabsorption of filtered phosphate in the proximal tubules of the kidney [Sato, 1997]. However, this mechanism was proposed before FGF23 was found to be a direct inhibitor of Iα-hydroxylase expression and it can be assumed that the effect of IV iron on Iα-hydroxylase expression is triggered via an increase in FGF23 concentration (as mentioned above), which leads to decreased production and increased degradation of 25-(OH)-Vitamin D Iα-hydroxylase [Shimada, 2011; Shimada, 2004a; Shimada, 2004b].

1.4. Symptoms and Signs of Hypophosphatemia

Although an FGF23-mediated decrease in serum phosphate after a single infusion of iron is usually transient, the risk of developing clinical symptoms and the actual clinical presentation is determined by the severity of hypophosphatemia and the time to recovery. Management of hypophosphatemia is within the judgment and discretion of the investigator.

Patients with hypophosphatemia typically report bone pain, general weakness, and asthenia [Okada, 1982;Schouten, 2009b; Mani, 2010; Shiraki, 1986; Sato, 1998; Suzuki, 1998; Konjiki, 1994; Shimizu, 2009; Yamamoto, 2013; Moore, 2013; Blazevic, 2014; Fierz, 2014; Vandemergel, 2014; Barea Mendoza, 2014; Poursac, 2015; Sangros Sahun, 2016]. In severe cases, proximal myopathy that also affects the diaphragm and rhabdomyolysis have been reported. The latter can also affect the heart or cause cardiomyopathy or cardiac arrhythmias [Bacchetta, 2012]. Rare manifestations include hemolysis, encephalopathy, seizures [Haglin, 2016]. The type of clinical manifestation expression is also dependent on the age at onset and the duration of hypophosphatemia. Young patients with long-standing hypophosphatemia typically present with growth retardation, delayed dentation and rickets [Elder, 2014]. In adults with hypophosphatemia persisting for several months, long-term complications such as osteomalacia can occur (Fig.2) [Gonciulea, 2017]. Presentation of osteomalacia can include bone pain, fractures, and pseudofractures, which may be difficult to diagnose on conventional X-ray.

Radiological findings are a coarse trabecular structure, and a loss of secondary trabeculae [Phan, 2016]. Low trauma fractures affecting the ribs or scapular “stress-“ fractures of the lumbar spine, pelvic structures, and long bones such as femur, tibia, or metatarsal are also common complications of osteomalacia. More sensitive diagnostic tests to identify looser zones, known as 'pseudofractures,' include computed tomography, magnetic resonance imaging, and bone scintigraphy. Bone biopsy showing increased ratio of osteoid to bone surface and reduced tetracycline labeling remains the gold standard for diagnosis, but is rarely performed due to its invasiveness. Although there is

no specific laboratory test for osteomalacia, mildly elevated total and bone-specific alkaline phosphatase in plasma have been repeatedly reported in the context of iron-induced hypophosphatemia [Phan, 2016].

2. SUB-STUDY OBJECTIVE

The objective of this sub-study is to characterize serum phosphorus levels over time in participants with heart failure with iron deficiency after dosing with FCM versus placebo.

3. SUB-STUDY RATIONALE AND DESIGN

3.1. Sub-Study Rationale

In two randomized clinical studies conducted with FCM (1VIT09030 and 1VIT09031), hypophosphatemia was an adverse drug reaction (treatment emergent adverse event assessed as related by the Investigator) that occurred in 2.1% (37/1775) of the study participants. Transient decreases in laboratory blood phosphorus levels (< 2 mg/dL) were observed in 27% (440/1638) of participants. Mean decreases from baseline in phosphorus occurred by Day 7, were highest at Day 14 and were returning toward baseline at Day 35 (1VIT09031) or Day 56 (1VIT09030). The objective of this sub-study is to characterize serum phosphorus levels over time in participants with heart failure with iron deficiency after dosing with FCM versus placebo.

3.2. Sub-Study Design

Participation in the sub-study is optional. Although all investigational sites are encouraged to participate, each study site's participation will be determined based on the feasibility of the site to participate. If a site decides to participate, all subsequent participants at the sites will be invited to enroll in the sub-study until enrollment of 110 study participants is achieved. Sites and participants have the option to perform sub-study visits either at the clinic or at a home visit.

A total of approximately 110 participants will be enrolled and the sample size has been determined based on the feasibility of enrollment. Sub-study duration will be up to 6 months for each participant. With this number of participants to be enrolled in the sub-study and the current knowledge on the course of hypophosphatemia with FCM, the evaluation after the initial dosing regimen only was determined to be sufficient to characterize the course of hypophosphatemia in participants with congestive heart failure. A separate informed consent form (ICF) for the sub-study will be signed by participants. Each participant in the sub-study will have additional blood samples collected at either clinic visits or at home visits on Days 14 ± 3, 21 ± 3, 35 ± 3, 63 ± 3, 91 ± 3, and 119± 3). These samples are in addition to the baseline (Day 0) and 6 month (Day 160-176) blood samples collected at the clinic visits for the main study.

3.3. Schedule of Events for Sub-Study

Table 1 Schedule of Events for Sub-Study

	Screening	Treatment Phase		Follow-up Phase							
Visit **Week of main-study**	**-28 to -1**	**Day 0**	**Day 7±2 1**	**Day 14±3* 2**	**Day 21±3* 3**	**Day 35±3* 5**	**Day 63±3* 9**	**Day 90±14† 13**	**Day 91±3* 13**	**Day 119±3* 17**	**Day 160-176, Day 180, Day 187, EOS**
	Participant follows the main study schedule of events							**Participant follows the main study**			**Participant follows the main study schedule of events**
Check that informed consent was signed at screening or at Day 0				X							
Inclusion/ Exclusion criteria				X							
Complete study activities as outlined in the main study Section 3.3	X							X			X
Serum Chemistry (see Section 6.5)				X	X	X	X		X	X	
1,25 $(OH)_2$ Vitamin D‡				X	X	X	X		X	X	
25 (OH) Vitamin D‡				X	X	X	X		X	X	
Parathyroid Hormone‡				X	X	X	X		X	X	

* In Clinic or Home visit
† Phone call or clinic visit
‡ Reminder that laboratory testing for 1,25 $(OH)_2$ Vitamin D, 1,25 $(OH)_2$ Vitamin D, and Parathyroid Hormone levels are also done outside the hypophosphatemia substudy at Day 0 and Day 160-176

4. PARTICIPANT SELECTION

4.1. Number and Type of Participants

Approximately 110 participants newly enrolled in the main 1VIT15043 study, who fulfill the inclusion criteria, do not meet any of the exclusion criteria and who have given written informed consent will be included.

4.2. Participant Selection

4.2.1. Inclusion Criteria

1. Demonstrate the ability to understand the requirements of the sub-study, willingness to abide by sub-study participation, and to return for the required assessments.

4.2.2. Exclusion Criteria

1. History of primary hypophosphatemic disorder (for example X-linked hypophosphatemia)
2. Baseline serum phosphate <2.5 mg/dL
3. Untreated primary hyperparathyroidism.

4.3. Participant Assignment and Randomization Process

Please follow guidance as detailed in the main body of the protocol.

4.4. Withdrawal from Study

Please follow guidance as detailed in the main body of the protocol.

5. CONCOMITANT MEDICATION

Please follow guidance as detailed in the main body of the protocol.

6. STUDY PROCEDURES

6.1. Treatment Phase

For Day 0 and Day 7 visits, follow guidance as detailed in the main body of the protocol.

6.2. Informed Consent

Check that the participant signed an informed consent form for the hypophosphatemia study at screening or at Day 0.

Prior to any study specific procedures, the investigator or his or her designee must explain to each participant the nature of the study, study purpose, procedures to be performed, expected duration, and the benefits and risks of study participation. After this explanation the participant must voluntarily sign an informed consent statement (Required Elements of Informed Consent, 21 CFR 50.25). The participant will be given a copy of the signed consent form.

6.3. Follow-up Phase

Clinic visits will be performed by study personnel.

Home visits will be performed by a contracted third party person qualified to collect blood or site personnel.

Once a home visit or clinic visit choice has been made, that patient must continue with that venue for the those visits for the duration of their sub-study participation.

After completing the 6-month sub-study, the participant returns to follow the main study protocol.

6.3.1. Sub-study Specific Visit Days 14 ± 3, 21 ± 3, 35 ± 3, 63 ± 3, 91 ± 3, 119 ± 3 (Clinic or Home Visits)

- Laboratory samples will be collected
  - Serum for:
    - Chemistry (see Section 6.5 for details)
    - 1,25 (OH)2 Vitamin D
    - 25 (OH) Vitamin D
  - Plasma for:
    - Parathyroid Hormone

Note that Visit Day 90±14 days (Phone call or Study visit) is a procedure in the main protocol to collect adverse event / serious adverse event assessment, including evaluation of potential endpoint events (blinded staff).

Study Visit Day 91±3 days will be an in-clinic visit (if the patient has chosen in-clinic visits) or a home visit (if the patient has chosen home visits) which will be performed by a qualified person to collect laboratory samples.

6.4. End of Sub-Study

Sub-study visits only occur within the first 180 days. No other sub-study dosing or blood collections will occur after that time.

6.5. Central Laboratory Assessment

Serum and plasma samples for laboratory analyses will be obtained at 1) Day 0 of the main study; 2) Days 14, 21, 35, 63, 91, and 119 at additional clinic visits or scheduled as home visits; 3) Day 160-178 of the main study. All serum and plasma laboratory testing shall be provided to the study personnel for review and assessment. The laboratory assessments will be determined as follows:

Chemistry: Sodium, potassium, chloride, BUN, creatinine, albumin, alkaline phosphatase, total bilirubin, GGT, AST, ALT, LDH, calcium, phosphate, glucose, bicarbonate and magnesium

Other: 1,25 dihydroxy Vitamin D; 25 hydroxy Vitamin D

Plasma: Parathyroid Hormone

7. ASSESSMENT OF SAFETY

7.1. Adverse Events

7.2. Reporting of Adverse Events

Please follow guidance for reporting of adverse events as detailed in the main body of the 1VIT15043 study protocol. For qualifying adverse events of hypophosphatemia, the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE Version 5.0) should be followed.

The serum phosphorus level normally ranges from 2.5-4.5 mg/dL or 0.80-1.45 mmol/L in adults. The reporting of hypophosphatemia, per the 2009 NCI CTCAE **Version 4.0**, is:

- Grade 1: mild (<LLN-2.5 mg/dL; <LLN-0.8 mmol/L),
- Grade 2: moderate (<2.5-2.0 mg/dL; <0.8-0.6 mmol/L),
- Grade 3: severe (<2.0-1.0 mg/dL; <0.6-0.3 mmol/L),
- Grade 4: potentially life threatening (<1.0 mg/dL; <0.3mmol/L; life-threatening consequences),
- Grade 5: death. (NCI 2009 [NIH, 2009]).

The updated 2017 NCI CTCAE **Version 5.0** includes the revised categorization and reporting of hypophosphatemia to the following:

- Grade 1: laboratory finding only and intervention not indicated;
- Grade 2: oral replacement therapy indicated;
- Grade 3: severe or medically significant but not immediately life-threatening - hospitalization or prolongation of existing hospitalization indicated;
- Grade 4: life-threatening consequences;
- Grade 5: death. (NCI 2017 [NIH, 2017]).

For this substudy, the analyses of changes in serum phosphate will be captured by laboratory changes, per NCI CTCAE version 4.0, and/ or safety reporting by any interventions determined and reported by the study investigator, per NCI CTCAE version 5.0. Please refer to Table 2: Hypophophosphatemia CTCAE Grade.

8. STATISTICS

Given the exploratory nature of this sub-study, the focus of the analyses will be on estimation rather than hypothesis testing. Continuous variables will be summarized in terms of the number of observations, mean, standard deviation, median, minimum, and maximum. Other descriptive statistics (e.g., quartiles, coefficient of variation) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages. Two-sided 95% confidence intervals will be presented, when appropriate.

Complete details of the analysis for this sub-study will be outlined in a Statistical Analysis Plan (SAP). This SAP will be completed prior to database lock.

8.1. Stratification/Randomization

Please follow guidance as detailed in the main body of the protocol.

8.2. Sample Size Rationale

No formal sample size calculations were made. Sample size for this sub-study was based on feasibility and practicality. The target sample size will be a total of approximately 110 participants, i.e., 55 participants per treatment group.

8.3. Analysis Population

The sub-study population will be defined as all participants in the Intent-to-Treat population who provided informed consent to participate in this sub-study.

Disposition, demographics, and baseline characteristics will be summarized for the sub-study population. Outcome measurements will be analyzed based on the available data from this population.

8.4. Endpoints and Definitions

8.4.1. Exploratory Phosphate Homeostasis Endpoints

The exploratory endpoints will be changes in laboratory values following study drug administration for:

1. Serum Phosphorous

2. 1, 25 dihydroxy Vitamin D (1,25[OH]2D)
3. 25 hydroxy Vitamin D (25[OH]D)
4. Plasma intact Parathyroid hormone

In addition to routine blood chemistry endpoints, the above laboratory studies will be summarized.

Details of the analysis of these exploratory endpoints will be described in the SAP.

8.5. Safety Analyses

8.5.1. Adverse Events

Adverse events will analyzed for the sub-study population as detailed in the main body of the 1VIT15043 study protocol.

8.5.2. Clinical Laboratory Tests

Clinical laboratory data will be summarized by scheduled visit using descriptive statistics. The actual values as well as the change from baseline will be summarized. Unscheduled visits will be excluded from these by-visit summaries. Maximum changes relative to baseline will be over all visits (both scheduled and unscheduled).

The time course for changes in serum phosphate will be evaluated and compared to that of other laboratory parameters.

Where applicable, the number and percent of participants with laboratory values outside pre-determined ranges will be summarized by scheduled visit. Unscheduled visits will be excluded from these by-visit summaries. The number and percent of participants with the laboratory values outside pre-determined ranges at any time during the sub-study will be summarized; and these summaries will be over all visits (both scheduled and unscheduled).

The proportion of participants with serum phosphate level <2.5 mg/dL (<0.8 mmol/L), per NCI CTCAE version 4, will be summarized by treatment group. Point estimates will be reported with exact two-sided 95% confidence intervals.

Full details will be described in the SAP.

9. ETHICS

9.1. Informed Consent

Informed consent must be obtained from each participant prior to sub-study participation. The informed consent will be provided to the participant in their native language. The consent form must be signed by the participant. Each investigational site must provide the Sponsor (or designee) with a copy of the Informed Consent approved by that site's

Institutional Review Board. The original signed consent form will be retained in the participant's study records, and a copy will be provided to the participant. The Clinical Monitor will assure that each Informed Consent meets the requirements of Parts 50.20 and 50.25 of Title 21 of the CFR, which outlines the basic elements of informed consent and International Conference on Harmonisation (ICH) guidelines. Translations of the informed consent must be certified by a qualified translator and their use must be documented.

The Informed Consent documents the information that the Investigator provides to the participant as well as the participant's agreement to participate. The Investigator will fully explain the nature of the study, along with the aims, methods, anticipated benefits, potential hazards and discomfort that participation might entail. The Informed Consent must be signed and dated by each participant before entering the study and prior to the performance of any study specific procedures.

9.2. Good Clinical Practice

The conduct of the study will conform with the recommendations for clinical studies in man as set out in the 2000 Edinburgh, Scotland Revision of the “Declaration of Helsinki”, the local legal requirements and the guidelines on “Good Clinical Practice”, [21 CFR Part 312 and ICH guidelines.

10. DATA HANDLING AND RECORD KEEPING

10.1. Case Report Form

The eCRFs will be completed for each participant on this study. The participants in this study will be identified only by a participant number and date of birth on these forms.

The eCRF used will be 21 CFR 11 compliant. The system used for data collection (eCRF) will meet all applicable regulatory requirements for recordkeeping and record retention as would be provided with a paper system. Security measures will be utilized to prevent unauthorized access to the data and to the computerized system. Changes made to data that are stored on electronic media will always require an audit trail, in accordance with 21 CFR 11.10(e).

The eCRFs must be reviewed and verified for accuracy by the Principal Investigator. An electronic copy of the eCRF will remain at the site at the completion of the study.

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Table 2 Hypophosphatemia CTCAE Grade

Hypophosphatemia: A disorder characterized by laboratory test results that indicate a low concentration of phosphates in the blood.					
CTCAE Grade:	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.*	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.	Life-threatening consequences; urgent intervention indicated.	Death related to AE.
From CTCAE v4.0 Metabolism and Nutrition Disorders - Hypophosphatemia: May 28, 2009: Page 45	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; Life-threatening consequences	Death
From CTCAE v5.0 Metabolism and Nutrition Disorders - Hypophosphatemia: November 27, 2017: Page 94	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences	Death

*A semi-colon indicates 'or' within the description of the grade.

Appendix 2: Protocol Amendment History

Overall Rationale for the Amendment (Version 2):

Affected Sections	Summary of Revisions Made	Rationale
Appendix 1	Added a sub-study protocol to evaluate hypophosphatemia.	To characterize serum phosphorus levels over time in participants with heart failure and iron deficiency after dosing with FCM.
Study synopsis and 4.2.1 Inclusion Criteria	Changes were made to inclusion criteria 2, 4, 5, 6, and 7. Details are provided below.	To specify certain time frames and values for inclusion and to further clarify certain inclusion criteria
Study synopsis and 4.2.2 Exclusion Criteria	Changes were made to exclusion criteria 3, 10, and 13. Details are provided below.	To specify certain time frames for, and to further clarify, certain exclusion criteria
8.10 Stopping Rules and Interim Analysis	The DSMB may recommend that the study continues as planned, discontinue the study or that the trial be continued with recommended changes to the protocol. The Executive Steering Committee will determine if an increase in sample size is warranted in order that to least 771 participants will experience an event of cardiovascular death or hospitalization for heart failure.	To clarify the roles of the DSMB and Steering Committee.

Detailed description of Protocol Amendment:

The deleted text (strikethrough) and the changed text (bold italics) is provided below.

Affected Sections	**Detailed Changes**
Signature page	[redacted]

	American Regent, Inc. [redacted]
Study synopsis: Design	Study drug administration will occur on Day 0 and Day 7 (±2) as an undiluted slow IV push, with additional study visits planned at 3 month intervals, and additional dosing administered every 6 months as applicable (see Section 3.1~~based on dose regimen below~~). ~~In a subset of sites, all participants will return for recurrent laboratory assessment (chemistry, hematology and iron indices) at Day 21 (± 7) after each course of investigational treatment.~~ For all participants, hematology, ferritin, and transferrin saturation (TSAT), with appropriate safety evaluations, to determine additional treatment, will occur at 6 month intervals. ***In a subset of sites, a sub-study will be conducted to characterize serum phosphate levels overtime in participants with heart failure and iron deficiency after dosing with FCM (see Appendix 1).***
Study synopsis: Inclusion Criteria and 4.2.1 Inclusion Criteria	2. Stable heart failure (NYHA II-IV) on maximally-tolerated background therapy (as determined by the site Principle Investigator) for at least ~~4 weeks with no dose changes in heart failure drugs during the last 2 weeks~~ ***2 weeks prior to randomization***. 4. Reduced left ventricular ejection fraction. Assessment must be performed at least 12 weeks after major cardiac surgical intervention including coronary artery bypass graft (CABG), valvular repair/replacement, or cardiac resynchronization therapy (CRT) device implantation. a Left ventricular ejection fraction ≤~~35~~ ***40***% obtained during the screening visit OR either of the following i Historical value of ejection fraction ≤~~35~~ ***40***%% within ~~12~~ ***24*** months of screening visit ii Historical value of ejection fraction ≤~~25~~ ***30***% % within ~~24~~ ***36*** months of screening visit 5. Hemoglobin >9.0 g/dL and <13.5 g/dL (females) or <15.0 g/dL (males) ***within 28 days of randomization***. 6. Serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%. ***Patients with screening ferritin <15 ng/ml must have documentation of an appropriate evaluation, as determined by the Principle Investigator, within 3 months of screening and prior to randomization.***

	7. Either documented hospitalization for heart failure within 12 months of enrollment or ~~screening visit~~ ***elevated N-terminal-pro-brain natriuretic peptide (NT-proBNP) within 90 days of randomization:*** ***a For patients in normal sinus rhythm:*** N-terminal-pro-brain natriuretic peptide (NT-proBNP) >600 pg/ml (or BNP >200 pg/mL) ~~for~~ ***b For*** patients ~~with normal sinus rhythm or~~ ***in atrial fibrillation:*** NT-proBNP >1000 pg/ml (or BNP >400 pg/mL) ~~for patients with atrial fibrillation~~.
Study synopsis: Exclusion Criteria and 4.2.2 Exclusion Criteria	~~1, Current or planned oral iron supplementation. Iron-containing multivitamins (<30 mgs /day) are permitted.~~ ~~4,~~ ***3.*** Acute myocardial infarction, acute coronary syndrome, transient ischemic attack, or stroke within ~~3 months~~ ***30 days*** of enrollment. ~~11,~~ ***10.*** ~~Known~~ ***Active*** gastrointestinal bleeding. ~~Patients with screening ferritin <15ng/ml must have an appropriate evaluation within 3 months of screening.~~ ***13. Concurrently in a study with investigational product.***
Study synopsis: Patient Assessments	**Efficacy and Safety Follow-up:** All participants will be followed from the time of randomization until completion of the trial. The last participant randomized will be followed for 12 months. After treatment on Day 0 and Day 7, participants will be evaluated at 3 month intervals (in person or via telephone), with additional dosing administered every 6 months as applicable (***see Section 3.1*** ~~based on dose regimen below~~)…..
Study synopsis: Study Sites:	Approximately ~~200~~ ***225***
3.1 Overall Study Design	After an initial screening period of up to 28 days, eligible participants will be stratified by region and randomized in a 1:1 ratio to FCM or placebo. Study drug administration will occur on Day 0 and Day 7 as an undiluted slow IV push, with additional study visits (in person or via telephone) planned at 3 month intervals, and additional dosing administered every 6 months as applicable (based on dose regimen below). ~~In a subset of sites, all participants will return for recurrent laboratory assessment (chemistry, hematology, and iron indices) at Day 21 (± 7) after each course of investigational treatment.~~ For all participants, hematology, ferritin and transferrin saturation (TSAT), with appropriate safety evaluations, to determine additional treatment, will occur at 6 month intervals ***In a subset of sites, a sub-study will be conducted to characterize serum phosphate levels overtime in participants with heart failure and iron deficiency after dosing with FCM (see Appendix 1).*** Initial treatment will occur on Day 0 and Day 7. On Day 0 and 7, Group A (FCM) will receive a 750 mg undiluted, blinded dose of IV FCM at the rate of approximately 100 mg (2 mL)/minute; Group B (placebo) will receive a blinded placebo (15 cc of normal saline) IV push at 2 mL/minute. Participants in Group A with body weight <50 kg (110 pounds) will have individual FCM doses adjusted to 15

	mg/kg, not to exceed an individual dose of 750 mgs or a cumulative dose of 1500 mg per treatment cycle. ***Placebo dosing will be adjusted for weight based on volume.***							
3.3 Schedule of Events	See changes below							
Study Procedures	**Screening**	**Treatment Phase**		**Follow-up Phase**				
Days	**-28 to -1**	**0**	**7±2**	**90 ±14[a,b,k,l]**	**160-*176* ~~178~~ [a,b]**	**180±7 [a,b]**	**187 ±7 [a,b]**	**EOS[c]**
Informed consent	X							
Inclusion/exclusion criteria	X	X[j]						
Demographics	X							
Targeted medical history	X							
Targeted Physical Exam		X[j]						X
Vital signs		X[d]	X[d]			X[d]	X[d]	X
Height (cm) & weight (kg)[e]		X[j]				X		
Urine ***or serum*** pregnancy test[f]		X[j]				X		X
~~Vitamin D,~~ ***1,25 (OH)$_2$ Vitamin D, 25 (OH) Vitamin D*** and PTH[k]		X			***X***			
Left ventricular ejection fraction	X[g]							
Randomization[n]		X						
Hematology laboratory[h]	X[p]	X			X			X
Chemistry laboratory[h]		X			X			X
Iron indices[h]	X	X			X			X
6 Minute Walk Test		X[j]				X[m]		
NT-proBNP[h]	X	X			***X***	~~X~~		X
Serious Adverse Event ***and Clinical Endpoint Event*** reporting		X	X	X	X	X	X	X
Concomitant medications	X	X	X			X	X	X
IV FCM/ IV Placebo[n]		X	X			X[i]	X[i]	

Abbreviations: EOS = End of Study; FCM = ferric carboxymaltose; IV = intravenous; NT-proBNP = N-terminal pro-brain natriuretic peptide; PTH = Parathyroid Hormone;

a Visits will be repeated every 180 days for the duration of the study

b ***At end of study, the visit*** ~~Visit~~ should not be performed if it would occur within 30 days of the EOS visit. ***If the participant is prematurely discontinued from the study and completing the EOS visit, the regular 6 or 12 month visit is needed to obtain the 6MWT.***

c EOS visit for all participants will be scheduled once the last participant has reached ~~6~~ ***12*** months on study and the anticipated number of outcome events (section 8) reaches ~~840~~

d ~~Vil~~ ***Vil*** study drug dosing days vital signs will be collected predose, immediately postdose, and 30 minutes postdose. ***Participants will be discharged from the site by the Investigator or***

his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed. e Height assessed at Day 0 only; weight assessed at Day 0 and prior to each dosing cycle. f. Females of childbearing potential g. Historical value can be used if performed within ~~12~~ ***24*** months of screening visit (or ~~24~~ ***36*** months if LVEF ≤~~25~~ ***30***%), must be performed at least 12 weeks after major cardiac intervention-including CABG, valvular intervention, or cardiac resynchronization therapy device implantation. h. ***The method of analysis of screening laboratory values will be by a central clinical laboratory. These laboratory values may also be analyzed locally.*** ~~Screening laboratory measures may be performed locally all~~ ***All*** other visits will be analyzed through a central laboratory i All participants randomized will be dosed every 6 months. Participants randomized to the FCM arm will be dosed as indicated based on blood counts (i.e. Hgb <13.5 g/dL [females] or <15.0 g/dL [males)]) and iron studies (i.e. serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%). Participants not meeting pre-specified laboratory criteria for blood counts and iron studies and all participants randomized to the placebo arm will be administered IV placebo infusion at each visit. The second of the 2 dosing visits should occur at Day 7±2 after the first dose. j. Prior to randomization k Only for participants at select sites performing additional chemistry labs ***(1,25 (OH)$_2$ Vitamin D, 25 (OH) Vitamin D and PTH)*** ~~on Day 21 (±7) post dosing~~ ***(sub-study)***. l. May be performed via telephone or in person. m. Performed at Day 180 and Day 360 visits only. n. To be performed by unblinded site personnel. All other procedures must be performed by personnel blinded to the treatment assignment ***p Hemoglobin only***	
4.4 Withdrawal from Study	At time of withdrawal from the study, procedures for the ***Termination*** ~~EOS~~ visit must be immediately performed regardless of whether the participant has completed study drug treatment….. In event of site closure, participants ~~will~~ ***may*** be asked to agree to follow up at another research site, if available, or for follow up by via a patient follow-up group
5.2 Drug Administration/ Regimen	**Group A:** Group A (FCM) will receive a 750 mg undiluted blinded dose of IV FCM at the rate of approximately 100 mg (2 mL)/minute on Day 0 and Day 7; ~~Participants in Group A with body weight <50 kg (110 pounds) will have individual FCM doses adjusted to 15 mg/kg,~~ not to exceed an individual dose of 750 mg or a cumulative dose of 1500 mg per treatment cycle. **Group B:** Group B (placebo) will receive a blinded placebo (15 cc of normal saline) IV push at 2 mL/minute on Day 0 and Day 7.

	Note: To avoid unblinding on the dose administration worksheet, if a participant is under 50 kg (110 pounds), the volume of FCM or placebo administered should be calculated based on the participant's weight, e.g. a 45 kg participant will receive a 13.5 mL dose of FCM or placebo.
6.2.1 Screening Visit	Each participant who has signed the informed consent and qualifies for inclusion will undergo the following clinical evaluations to confirm eligibility for the study (all procedures to be performed by blinded study personnel): • Demographic and medical history including NYHA heart failure class and prior heart failure hospitalizations • Left ventricular ejection fraction (historical values may be used if performed within ~~12~~ ***24*** months of the screening visit, or ~~24~~ ***36*** months if LVEF ≤~~25~~ ***30***%) must be performed at least 12 weeks after major cardiac intervention-including CABG, valvular intervention, or cardiac resynchronization therapy device implantation • Blood samples for hematology, iron indices, and NT-proBNP (~~local~~ ***central*** laboratory)
6.3.1 Day 0 Visit	For all participants (all procedures to be performed by blinded study personnel): • Verify all inclusion and exclusion criteria • Height and weight • Targeted physical exam • Blood samples for central lab hematology, chemistries and iron indices for all participants; ~~Vitamin D, PTH~~ ***1,25 (OH)$_2$ Vitamin D, 25 (OH) Vitamin D and PTH*** for participants ***of the hypophosphatemia sub-study*** ~~at sites selected for post dose chemistry follow-up visits.~~ • Review concomitant medications • Urine ***or serum*** pregnancy test (women of childbearing potential only) ***Note: To avoid unblinding on the dose administration worksheet, if a participant is under 50 kg, the volume of FCM or placebo administered should be calculated based on the participant's weight, e.g. a 45 kg participant will receive a 13.5 mL dose of FCM or placebo.*** Group A: • Verify amount of single FCM dose (15mg/kg up to a maximum dose of 750 mg) (unblinded staff) • Pre-administration, obtain heart rate, blood pressure, and body temperature (blinded staff) • Administer FCM as a slow IV injection at the rate of approximately 2 mL /minute taking appropriate measures to ensure the participant and all blinded staff members remain

	blinded to the treatment being administered (unblinded staff)
	• Document start and stop time of FCM administration and the total dose and volume administered (unblinded staff)
	• Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after FCM administration (blinded staff). ***Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.***
	Group B:
	• Pre-administration, obtain heart rate, blood pressure, and body temperature (blinded staff)
	• Administer a 15 mL dose of placebo (normal saline) as a slow IV injection at the rate of approximately 2 mL /minute taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff).
	  • Document start and stop time of placebo administration and the total volume administered (unblinded staff).
	  • Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after placebo administration (blinded staff). ***Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.***

6.3.2 Day 7 Visit	All participants will return to the clinic for study drug dosing on Day 7(±2). Prior to the administration of the study drug, the participant will be evaluated clinically to assess the development of clinically significant conditions that may contraindicate dosing. ***Note: To avoid unblinding on the dose administration worksheet, if a participant is under 50 kg, the volume of FCM or placebo administered should be calculated based on the participant's weight, e.g. a 45 kg participant will receive a 13.5 mL dose of FCM or placebo.*** Group A participants the following will be performed: • Verify amount of single FCM dose (15mg/kg up to a maximum dose of 750 mg) (unblinded staff) • Pre-administration, obtain heart rate, blood pressure, and body temperature (blinded staff) • Administer FCM as a slow IV injection at the rate of approximately 2 mL /minute taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff) • Document start and stop time of FCM administration and the total dose and volume administered (unblinded staff) • Post-administration, obtain heart rate and blood pressure

	immediately after and 30 minutes after FCM administration (blinded staff). ***Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.***
	Group B participants the following will be performed:
	• Pre-administration, obtain heart rate, blood pressure, and body temperature (blinded staff)
	• Administer a 15 mL dose of placebo (normal saline) as a slow IV injection at the rate of approximately 2 mL /minute taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff).
	  • Document start and stop time of placebo administration and the total volume administered (unblinded staff).
	  • Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after placebo administration (blinded staff). ***Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.***

~~6.4.1 Chemistry Laboratory Collection Subset -Day 21 (± 7)~~	~~In a subset of sites approximately 500 participants, will have central lab clinical laboratories (chemistry, hematology and iron indices) collected following the initial and each subsequent course (approximately every 6 months) of study drug treatment (FCM or Placebo). The participants will have chemistry laboratories collected 21±7 days post the first treatment for that course (i.e. Study Days 21±7, 201±7, 381±7, 561±7, 741±7, 921±7…EOS). (blinded staff)~~
~~6.4.3~~ ***6.4.2*** 6 Month Laboratory Evaluation	Participants will receive an additional course of study medication every 180 (±7) days. Within ~~2~~ ***4*** to 20 days prior to these scheduled dosing visits, all participants will return to the clinic to obtain central lab hematology, chemistry, and iron indices laboratory tests. ***1,25 $(OH)_2$ Vitamin D, 25 (OH) Vitamin D and PTH for participants of the hypophosphatemia sub-study.*** (Blood to be collected by blinded staff)
~~6.4.4~~ ***6.4.3*** Additional Study Drug Dosing (Every 6 Months)	All participants will be dosed every 6 months. At each 6-month interval, a course of 2 doses of study drug will be administered as described above for Day 0 and Day 7 (Section 6.3). For group A, FCM will be administered if Hgb < 13.5 g/dL (females) or <15.0 g/dL (males) and serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%; ***observe carefully that*** placebo (normal saline) will be administered to participants in the FCM group who do not meet the above criteria. All group B participants will receive placebo (normal saline).
~~6.4.4.1~~ ***6.4.3.1***	6 Month Dosing Visit #1 (Days 180±7, 360±7, 540±7, ~~660~~ ***720***±7, ~~840~~ ***900***±7, ~~1,020~~ ***1,080***±7…EOS)

	• Weight
	• Urine ***or serum*** pregnancy test (women of childbearing potential only)
	
	Note: To avoid unblinding on the dose administration worksheet, if a participant is under 50 kg, the volume of FCM or placebo administered should be calculated based on the participant's weight, e.g. a 45 kg participant will receive a 13.5 mL dose of FCM or placebo.
	For Group A participants the following will be performed:
	
	• Administer FCM or placebo as a slow IV injection at the rate of approximately 2 mL /minute. Appropriate measures must be taken to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff)
	  • Document start and stop time of IV administration, and the total dose and volume administered (unblinded staff)
	  • Post-administration of FCM, obtain heart rate and blood pressure immediately after and 30 minutes after FCM administration (blinded staff). ***Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.***
	
	For Group B participants the following will be performed:
	
	• Pre-administration, obtain heart rate, blood pressure and body temperature. (blinded staff)
	• Administer a 15 mL dose of placebo (normal saline) as a slow IV injection, at the rate of approximately 2 mL /minute. Taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff)
	
	  • Document start and stop time of placebo administration and the total volume administered. (unblinded staff)
	  • Post-administration of placebo, obtain heart rate and blood pressure immediately after and 30 minutes after placebo administration (blinded staff). ***Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.***

~~6.4.4.2~~ ***6.4.3.2***	Six Month Dosing Visit #2 (Days 187±7, 367±7, 547±7, ~~667~~ ***727***±7, ~~847~~ ***907***±7, ~~1,027~~ ***1,087***±7…EOS) ***Note: To avoid unblinding on the dose administration worksheet, if a participant is under 50 kg, the volume of FCM or placebo administered should be calculated based on the participant's weight, e.g. a 45 kg participant will receive a 13.5 mL dose of FCM or placebo.***

	For Group A participants the following will be performed:
	• Verify amount of single FCM dose (15mg/kg up to a maximum dose of 750 mg) or placebo (15 mL). Note: participant should receive the same product (FCM or placebo) as received at the first dose of this course of treatment. (unblinded staff)
	• Pre-administration, obtain heart rate, blood pressure, and body temperature. (blinded staff)
	• Administer FCM or placebo as a slow IV injection at the rate of approximately 2 mL /minute. Taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff).
	  • Document start and stop time of IV administration, and the total dose and volume administered (unblinded staff)
	  • Post-administration of FCM, obtain heart rate and blood pressure immediately after and 30 minutes after FCM administration (blinded staff). ***Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.***
	For Group B participants the following will be performed:
	• Pre-administration, obtain heart rate, blood pressure and body temperature. (blinded staff)
	• Administer a 15 mL dose of placebo (normal saline) as a slow IV injection, at the rate of approximately 2 mL /minute. Taking appropriate measures to ensure the participant and all blinded staff members remain blinded to the treatment being administered (unblinded staff)
	  • Document start and stop time of placebo administration and the total volume administered. (unblinded staff).
	  • Post-administration, obtain heart rate and blood pressure immediately after and 30 minutes after placebo administration (blinded staff). ***Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.***

6.5 End of Study Visit	End of study visits for all participants will be scheduled once the last participant has reached 12 months on study and at least 771 participants have experienced an event of cardiovascular death or hospitalization for heart failure. ~~When possible, the~~ ***The*** participants should return to the clinic and the following will be performed by blinded study staff: • Targeted physical exam • Vital signs including BP and heart rate • Blood samples for central lab hematology, chemistries, iron indices and NT-proBNP. • Urine ***or serum*** pregnancy test (women of childbearing potential

	only)
6.6 Laboratory Assessments	Serum samples for laboratory analyses must be obtained at all appropriate visits. ***The method of analysis of screening*** ~~Screening~~ laboratory values will be ~~analyzed~~ ***by a central clinical laboratory. These laboratory values may also be analyzed*** locally. All other visit laboratory samples will be analyzed by a central clinical laboratory. All laboratory testing will be provided to the investigator or his/her medically qualified designee for review and assessment. Post dose iron indices and serum phosphorus results will be provided to the designated unblinded investigator for assessment. The laboratory assessments will be determined as listed in Section 3.3: Other: ~~Vitamin D, Parathyroid Hormone,~~ ***1,25 (OH)$_2$ Vitamin D, 25 (OH) Vitamin D, PTH, and*** NT-proBNP
7.2 Reporting of Adverse Events	For the purposes of this study, any AE that does not meet the protocol definition of a serious AE is considered non-serious. Non-serious AEs will not be collected for this trial, except for AEs leading to cessation of study medication. ***Adverse experiences will be elicited by nonspecific questions such as "Have you noticed any problems?" Participants will be encouraged to report adverse events at their onset.*** Disease progression can be considered as a worsening of a patient's clinical condition attributable to the disease in the patient population for which the study medication is being studied. It may be an increase in the severity of the disease under study, and/or increases in the symptoms of the disease. ***These also include the events listed in Section 7.4, "Reporting of Events that May Require Adjudication."*** The development of the following cardiovascular disease events will be recorded in the eCRF, however they should be considered as disease progression and will not be reported as an AE/SAE during the study unless determined to be clinical endpoints. ***1. Supraventricular arrhythmia (e.g., atrial fibrillation) requiring urgent/emergent intervention*** ***2. Ventricular arrhythmia (e.g., ventricular tachycardia or fibrillation) requiring urgent/emergent intervention including ICD shock*** ***3. Renal failure requiring urgent/emergent intervention (e.g., initiation of dialysis)*** ~~These ***also*** include the events listed in Section 7.4, "Reporting of Events that May Require Adjudication." Adverse experiences will be elicited by nonspecific questions such as "Have you noticed any problems?" Participants will be encouraged to report adverse events at their onset.~~

	These three events will be documented on a dedicated form in the eCRF and they will be reported to the DSMB. An analysis as well as summary data tables of these events will be provided in the safety section of the clinical study report which will also include a rationale for exclusion of these events from AE or SAE reporting. Data files containing information about the above events will be included in the Regulatory submission in addition to hyperlinks or other means to easily direct reviewers to the location of the data.
7.3 Serious Adverse Events	Suspected clinical endpoint events that may traditionally meet the definition of an SAE, will not be reported by the sites in this trial as an SAE***, but will be reported as a suspected clinical endpoint***. Those events will therefore not ~~to~~ be reported to the sponsor's Drug Safety Surveillance department. Certain events of interest ***(supraventricular arrhythmia, ventricular arrhythmia, and renal failure)*** that are related to heart failure (serious and non-serious) ~~and selected expected (described in the label) serious side effects of the study drug~~ will be listed on the eCRF and not be reported by the site as an SAE. These events will be monitored by the Data Safety Monitoring Board to ensure participant safety. Additionally suspected clinical events that are reviewed by the CEC but do not meet the criteria of an endpoint event will ***then*** be reviewed by the safety surveillance team for possible unreported SAEs. Reporting: Any SAE as defined by this protocol, starting with the time of randomization, that is to be reported (as outlined in the section above) must be reported immediately (by the end of the next business day) to American Regent, Inc. This occurs through entry into the eCRF by the local investigator/coordinator and completing the SAE module. In the event that the eCRF module is not available ***and paper forms have not been provided for use,*** the investigator will contact the Study Safety Monitor at
7.4 Reporting of Suspected Study Endpoint Events that May Require Adjudication	Therefore, any event that may possibly constitute one of these endpoints will be evaluated by the CEC Committee by a procedure ~~to be~~ described in separate documentation. A description of the CEC Committee and the definitions of the above clinical endpoints may be found in Section 10.2.
8.5 Secondary Outcomes	~~An~~ ***A Clinical Events Classification (CEC)*** ~~endpoint adjudication committee~~ ***Committee*** at DCRI will review all potential events comprising all endpoints, and make the final determination whether an endpoint event has occurred for each participant (See Section 10.2).
8.10 Stopping Rules and Interim Analysis	A Data and Safety Monitoring Committee (DSMB), with statistical support from DCRI will review safety data, including a tally of the composite outcome events at least every 6 months (See Section 10.3). The DSMB can recommend stopping the study for safety concern at any point. In addition, one interim analysis is planned to

	determine if an early stopping for an overwhelming efficacy should be recommended ~~or if an increase in sample size is warranted~~. This analysis will be conducted after 2250 (75%) participants have been enrolled. Significance level will be set at 0.0001 for this analysis, resulting in an adjusted significance level for the final analysis of 0.0099 for the primary endpoint and 0.0499 for the first secondary endpoint, preserving the overall significance at 0.01 and 0.05, respectively. Conditional power will be estimated based on data accrued to date and presented to the DSMB. The DSMB may recommend that the study continues as planned, ~~is stopped for overwhelming efficacy or that the sample size or trial duration is increased to achieve at least 80% conditional power but not by more than 50% of the original sample size or duration~~ ***discontinue the study or that the trial be continued with recommended changes to the protocol. The Executive Steering Committee will determine if an increase in sample size is warranted in order that at least 771 participants will experience an event of cardiovascular death or hospitalization for heart failure.***
9.8.1 Case Report Form	The eCRFs will be completed for each participant on this study. The participants in this study will be identified only by a participant number ***and date of birth*** on these forms.
10.1 Steering Committee (SC)	The SC will be responsible for oversight of the study. The SC chair will be Dr. Adrian Hernandez of DCRI. The SC will consist of ~~4-8~~ ***6-12*** members including the chair, primarily from academic institutions, ~~as well as~~ ***in addition to*** representation of the Sponsor. The SC will consist of experts in heart failure as well as cardiovascular outcomes trials.
10.2.1.6 Death Due to Other Cardiovascular Causes	Death due to Other Cardiovascular Causes refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolus***, deep vein thrombosis,*** ~~or~~ peripheral arterial disease***, or aortic aneurysm***).
10.2.2.4 Other Cardiovascular Hospitalizations	Urgent and unscheduled hospitalizations for other cardiovascular causes that do not meet the criteria for the specific events listed above will be classified as hospitalization for other cardiovascular causes. Examples would include***, but are not limited to,*** hospitalization for cardiac chest pain that does not meet the criteria for MI, ***hospitalization for carotid events, hospitalization for deep vein thrombosis,*** hospitalization for arrhythmias, hospitalization for pulmonary embolism, etc. These hospitalizations will not be further sub-classified by the CEC.
13.0 Appendices	Appendix 1: Protocol for hypophosphatemia study was added
	Appendix 2: Added protocol amendment history

Overall Rationale for the Amendment (Version 3):

Affected Sections	Summary of Revisions Made	Rationale
Study synopsis and 4.2.2 Exclusion Criteria	Changes were made to exclusion criteria 4 to include participants with mitral regurgitation due to left ventricular dilatation without planned intervention	This exclusion criteria was leading to exclusion of eligible participant's into the study
Study Synopsis and 4.2.2 Exclusion Criteria	Added exclusion criteria 14	To not allow participants with current COVID-19 infection into the study.
4.5 Discontinuation from Study Drug	Added the following sentence: Participants who discontinue study drug for reasons unrelated to safety may resume study drug if deemed appropriate by the Principal Investigator**.**	To provide guidance to the sites.
4.5 Discontinuation from Study Drug	Added a definition for a participant permanently discontinued from the study.	To provide guidance to the sites.
Appendix 1, Section 3.2	Added that sites and participants have the option to perform sub-study visits either at the clinic or at a home visit.	To provide the sites and participants flexibility in deciding how sub-study visits will be conducted.
Appendix 1, Section 7.2: Reporting of Adverse Events and Table 2	The changes in serum phosphate will be captured by laboratory changes, per NCI CTCAE version 4, and any interventions per the study investigator, per NCI CTCAE version 5.	Inclusion of the most CTCAE version for the investigator's awareness.
Appendix 1, Guidance for Managing Hypophosphatemia	This section has been removed	Management of hypophosphatemia is within the judgment and discretion of the investigator.

Detailed description of Protocol Amendment (Version 3):

The deleted text (strikethrough) and the changed text (bold italics) is provided below.

Affected Sections	**Detailed Changes**
Signature page	[redacted]

Study Synopsis: Inclusion Criteria and 4.2.1 Inclusion Criteria	1. Adult (≥18 years of age) able to provide ***signed, written*** informed consent.
Study Synopsis: Exclusion Criteria and 4.2.2 Exclusion Criteria	4. Uncorrected severe aortic stenosis, severe valvular regurgitation ***(except mitral regurgitation due to left ventricular dilatation without planned intervention),*** or left ventricular outflow obstruction requiring intervention.
Study Synopsis: Exclusion Criteria and 4.2.2 Exclusion Criteria	***14. Current COVID-19 infection***.
Study Synopsis: Study Sites:	Approximately ~~225~~ ***300***
3.3 Schedule of Events:	See changes below

Study Procedures	**Screening**	**Treatment Phase**		**Follow-up Phase**				
Days	**-28 to -1**	**0**	**7±2**	**90 ±14[a,b,,l]**	**160-176 [a,b]**	**180±7 [a,b]**	**187 ±7 [a,b]**	**EOS[c]**
Informed consent	X							
Inclusion/exclusion criteria	X	X[j]						
Demographics	X							
Targeted medical history	X							
Targeted Physical Exam		X[j]						X
Vital signs		X[d]	X[d]			X[d]	X[d]	X
Height (cm) & weight (kg) [e]		X[*ej*]				X[*e*]		
Urine or serum pregnancy test[f]		X[*fj*]				X[*f*]		X[*f*]
1,25 $(OH)_2$ Vitamin D, 25 (OH) Vitamin D and PTH[k]		X[*k*]			X[*k*]			
Left ventricular ejection fraction	X[g]							
Randomization[~~a~~]		X[*n*]						
Hematology laboratory[~~h~~]	X[*h*p]	X[*h*]			X[*h*]			X[*h*]
Chemistry laboratory[~~h~~]		X[*h*]			X[*h*]			X[*h*]
Iron indices[~~h~~]	X[*h*]	X[*h*]			X[*h*]			X[*h*]
6 Minute Walk Test		X[j]				X[m]		
NT-proBNP[~~h~~]	X[*h*]	X[*h*]			X[*h*]			X[*h*]
Serious Adverse Event and Clinical Endpoint Event reporting		X	X	X	X	X	X	X
Concomitant medications	X	X	X			X	X	X
IV FCM/ IV Placebo[~~a~~]		X[*n*]	X[*n*]			X[i*n*]	X[i*n*]	

h. The method of analysis of screening laboratory values will be by a central clinical laboratory. ~~These laboratory values may also be analyzed locally.~~ All ~~other~~ visits will be analyzed through a central laboratory

4.4 Withdrawal from Study	In event of site closure, participants may be asked to agree to follow up at another research site, if available, or for follow up by ~~via~~ a patient follow-up group
4.5 Discontinuation from Study Drug	Participants may elect to discontinue study drug, but wish to remain in the study for follow-up. In those situations, patients will be asked to continue the normal clinical trial schedule for ascertainment of endpoint and safety events. ***Participants who discontinue study drug for reasons unrelated to safety may resume study drug if deemed appropriate by the Principal Investigator.*** If a participant permanently discontinues ***investigational product (drug is considered to be permanently discontinued after the second missed dosing cycle with continued follow-up in the trial)*** ~~investigational product~~ and is unable to attend visits in-person, he/she will be contacted by telephone, or other methods to assess study outcomes and vital status, unless the participant has specifically withdrawn consent for all forms of contact…..
5.1 Formulation, Packaging and Storage	Placebo (normal saline) will be supplied as 15 ml ***fill in 20 ml*** vials. All IV study drugs (FCM and Normal Saline) must be kept in a secure place at the investigational site, and stored at room temperature (see USP). The study medication should not be frozen. Vials may not be used for more than 1 dose, or for more than 1 participant. All vials (used and unused) should be kept by the study staff for reconciliation by the monitor ***unless the site is unable to retain them and documentation (site or institution process or procedures, or SOPs, for example) is present.*** Following reconciliation, sites may destroy used and unused study drug on site using local procedures, provided a drug destruction policy is in place, or it may be returned to American Regent, Inc.
5.2 Drug Administration/ Regimen	**Group A:** Group A (FCM) will receive a 750 mg undiluted blinded dose of IV FCM at the rate of approximately 100 mg (2 mL)/minute ***(approximately 7 minutes 30 seconds)*** on Day 0 and Day 7, not to exceed an individual dose of 750 mg or a cumulative dose of 1500 mg per treatment cycle. **Group B:** Group B (placebo) will receive a blinded placebo (15 cc of normal saline) IV push at 2 mL/minute ***(approximately 7 minutes 30 seconds)*** on Day 0 and Day 7.
5.5 Concomitant Medication	All Concomitant medications will be recorded in the eCase Report Form (eCRF).

	Note: Oral iron supplementation is permitted prior to screening and during the course of the study.
6.2.1 Screening Visit	• Enter participant in the Interactive Response Technology (IRT) system to obtain screening number. • Participants who do not meet study entry criteria should be entered into the IRT system as a screen failure. ~~If all entry criteria can be verified qualified participants may be randomized and proceed to the Day 0 visit on the same day as the screening visit.~~
6.3.1 Day 0 Visit	For all participants (all procedures to be performed by blinded study personnel): • Blood samples for central lab hematology, chemistries and iron indices for all participants; ***For Hypophosphatemia Sub-Study participants only:*** 1,25 $(OH)_2$ Vitamin D, 25 (OH) Vitamin D and PTH ~~for participants of the hypophosphatemia sub-study~~. Note: To avoid unblinding on the dose administration worksheet, if a participant is under 50 kg, the volume of FCM or placebo administered should be calculated based on the participant's weight, e.g. a 45 kg participant will receive a 13.5 mL dose of FCM or placebo. ***Note: All IV injection start and stop times are to be captured in hh:mm:ss format.***
6.6 Laboratory Assessments	Serum samples for laboratory analyses must be obtained at all appropriate visits. The method of analysis of screening laboratory values will be by a central clinical laboratory. ~~These laboratory values may also be analyzed locally.~~ All ~~other~~ visit laboratory samples will be analyzed by a central clinical laboratory. All laboratory testing will be provided to the investigator or his/her medically qualified designee for review and assessment. Post dose iron indices and serum phosphorus results will be provided to the designated unblinded investigator for assessment. The laboratory assessments will be determined as listed in Section 3.3:
7.1 Adverse Events	**Timing:** Adverse events and serious adverse events will be reported, as described below in Section 7.2, from the time of randomization through the end of study. Adverse events for participants randomized and who terminate ***the study*** early ***or permanently discontinue study drug*** (***Section 4.5)*** will be reported for 30 days after the last treatment. ***All reported SAEs should be followed until no longer serious or return to baseline grade.***

7.2 Reporting of Adverse Events	For the purposes of this study, any AE that does not meet the protocol definition of a serious AE is considered non-serious. ***All SAEs and only AEs leading to study discontinuation will be collected in this study. Non-serious AEs that do not lead to study drug discontinuation are not being collected in this study."*** ~~Non-serious AEs will not be collected for this trial, except for AEs leading to cessation of study medication.~~ Adverse experiences will be elicited by nonspecific questions such as "Have you noticed any problems?" Participants will be encouraged to report adverse events at their onset.
8. Statistic***al Methods***	All statistical tests will be two-tailed. Type I error of 0.05 is assumed unless otherwise specified. No adjustments for multiple testing will be made. ***Complete details for the summary and statistical analysis of data to be collected will be documented in a Statistical Analysis Plan (SAP), which will be finalized prior to unlocking of the study base. The important elements of the planned methods are provided below.***
9.4 Advertisement for Participant Recruitment	All advertisement for participant recruitment must be reviewed and approved by the Sponsor and the site's IRB prior to implementation. Advertisement may include but is not limited to: newspaper, fliers, radio, ~~and~~ television***, and the use of social media by the central ad campaign***. Any compensation to the participant included in the advertisement must be identical to the compensation stated in the IRB-approved informed consent.
Appendix 1, Cover Page	**Sponsor** American Regent, Inc. Clinical Research and Development 800 Adams Avenue, Suite ***200*** ~~100~~ Norristown, PA 19403
Appendix 1, Contact Person for the Sub-study	[redacted]

	[redacted]
Appendix 1, List of Abbreviations	ICF Informed Consent Form
Appendix 1, Section 1.1, Pathophysiology	~~The serum phosphorus level normally ranges from 0.80-1.45 mmol/L or approximately 2.5-4.5 mg/dL in adults. Hypophosphatemia is defined per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) as mild (0.6-<0.8 mmol/L or 2.0-<2.5 mg/dL), moderate (0.3-<0.6 mmol/L or 1.0-<2.0 mg/dL), or severe (<0.3 mmol/L or <1.0 mg/dL) (NCI 2009 NIH, 2009]. Symptoms usually occur when serum phosphorus level decrease below 0.32 mmol/l [Prinsloo, 2016].~~ ***Phosphorus homeostasis is complex and is regulated by several hormones.*** ~~A decrease in the level of serum phosphorus (hypophosphatemia) should be distinguished from a decrease in total body content of phosphate (phosphate deficiency).~~ Hypophosphatemia can occur in the presence of low, normal, or high total body phosphate. In the latter ***two*** ~~2~~ instances, a shift from the extracellular pool into the intracellular compartment is a major contributory factor. ~~Phosphorus homeostasis is complex and is regulated by several hormones.~~ Parathyroid hormone causes phosphate to be released from bone and inhibits renal reabsorption of phosphate, resulting in phosphaturia….
Appendix 1, Section 1.2, Increased FGF23	These finding suggest the IDA increases ***cFGF23*** ~~cFHF23~~ levels, and that certain iron preparations temporarily increase iFGF23 levels.
Appendix 1, Section 1.4, Symptoms and Signs of Hypophosphatemia	Although an FGF23-mediated decrease in serum phosphate after a single infusion of iron is usually transient, the risk of developing clinical symptoms and the actual clinical presentation is determined by the severity of hypophosphatemia and the time to recovery. ~~The Common Terminology Criteria for Adverse Events has graded the severity of hypophosphatemia as mild. (<LLN-2.5 mg/dl; <LLN-0.8 mmol/1), moderate (<2.5-2.0 mg/dl; <0.8-0.6 mmol/1), severe (<2.0-1.0 mg/dl; <0.6-0.3 mmol/1), or potentially life threatening (< 1.0 mg/dl; <0.3 mmol/1; life-threatening consequences) [Zoller, 2017].~~ ***Management of hypophosphatemia is within the judgment and discretion of the investigator.***
Appendix 1, Section 2, Sub-Study Objectives	The objective of this sub-study is to characterize serum phosphorus levels over time in participants with heart failure ***with*** ~~and~~ iron deficiency after dosing with FCM ***versus placebo***
Appendix 1, Section 3.1, Sub-Study Rationale	In two randomized clinical studies conducted with FCM (1VIT09030 and 1VIT09031), hypophosphatemia was an adverse drug reaction (treatment emergent adverse event assessed as related by the Investigator) that occurred in 2.1% (37/1775) of the ***study*** participants. Transient decreases in laboratory blood phosphorus

	levels (< 2 mg/dL) were observed in 27% (440/1638) of participants. Mean decreases from baseline in phosphorus occurred by Day 7, were highest at Day 14 and were returning toward baseline at Day 35 ***(1VIT09031) or Day*** ~~day~~ ***56 (1VIT09030)***. The objective of this sub-study is to characterize serum phosphorus levels over time in participants with heart failure ***with*** ~~and~~ iron deficiency after dosing with FCM ***versus placebo***.
Appendix 1, Section 3.2, Sub-Study Design	Participation in the sub-study is optional. Although all investigational sites are encouraged to participate, each ***study*** site's participation will be determined based on the feasibility of the site to participate. ***If*** ~~Once~~ a site decides to participate, all subsequent participants at the sites will be invited to enroll in the sub-study ***until enrollment of 110 study participants is achieved. Sites and participants have the option to perform sub-study visits either at the clinic or at a home visit.*** A total of approximately 110 participants will be enrolled ***and*** ~~in the sub-study~~ ***the*** ~~The~~ sample size has been ***determined*** ~~chosen~~ based on the feasibility of enrollment ~~in the sub-study~~. Sub-study duration will be up to 6 months for each participant. With this number of participants to be enrolled in the sub-study and the current knowledge on the course of hypophosphatemia with FCM, the evaluation after the initial dosing regimen only was determined to be sufficient to characterize the course of hypophosphatemia in participants with congestive heart failure. A separate ***informed consent form (***ICF***)*** for the sub-study will be signed by participants. Each participant in the sub-study will have additional ***blood*** samples collected at ***either*** ~~the~~ ***clinic visits or at*** ~~a~~ home visits on Days 14 ± 3, 21 ± 3, 35 ± 3, 63 ± 3, 91 ± 3, and 119± 3). ***These samples are in addition to the baseline (Day 0) and 6 month (Day 160-176) blood samples collected at the clinic visits for the main study.***

Appendix 1, Section 3.3 Schedule of Events for Sub-Study	See changes below

Table 1 Schedule of Events for Sub-Study

	Screening	**Treatment Phase**		**Follow-up Phase**							
Visit **Week of main-study**	**-28 to -1**	**Day 0**	**Day 7± 2 1**	**Day 14±3 ~~2~~* 2**	**Day 21±3* 3**	**Day 35±3* 5**	**Day 63±3* 9**	**Day 90±14† 13**	**Day 91±3* 13**	**Day 119±3* 17**	**Day 160-176, Day 180, Day 187, EOS**

* ***In Clinic or*** Home visit
† Phone call or clinic visit
‡ Reminder that laboratory testing for 1,25 $(OH)_2$ Vitamin D, 1,25 $(OH)_2$ Vitamin D, and Parathyroid Hormone levels are also done outside the hypophosphatemia ***sub-***study at Day 0 and Day 160-176

Appendix 1, Section 4.1, Number and Type of Participants	Approximately 110 participants newly enrolled in the main ***1VIT15043*** study, who fulfill the inclusion criteria, do not meet any of the exclusion criteria and who have given written informed consent will be included.
Appendix 1, Section 4.2.1, Inclusion Criteria	1. Demonstrate the ability to understand the requirements of the sub-study, willingness to abide by sub-study ***participation*** ~~restrictions~~, and to return for the required assessments
Appendix 1, Section 4.2.2, Exclusion Criteria	2. ***Baseline serum phosphate*** ~~Hypophosphatemia~~ <2.5 mg/dL
Appendix 1, Section 6.2, Informed Consent	Prior to any study specific procedures, the investigator or his or her designee must explain to each participant the nature of the study, ***study*** ~~its~~ purpose, procedures to be performed, expected duration, and the benefits and risks of study participation….
Appendix 1, Section 6.3, Follow-up Phase	***Clinic visits will be performed by study personnel.*** ***Home visits will be performed by a contracted third party person qualified to collect blood or sitepersonnel.*** ***Once a home visit or clinic visit choice has been made, that patient must continue with that venue for those visits for the duration of their sub-study participation.*** After completing the 6-month ***sub-study*** ~~sub-cohort follow-up phase~~, the participant returns to follow the main ***study*** protocol. ~~Home visits will be performed by a contracted third party person qualified to collect blood. They will not be performed by study personnel.~~
Appendix 1, Section 6.3.1, ***Sub-Study Specific*** Visit Days 14 ± ***3***, 21 ± ***3***, 35 ± ***3***, 63 ± ***3***, 91 ± ***3***, 119 ± ***3*** (***Clinic or*** Home Visits)	Study Visit Day 91±3 days ~~may~~ ***will be an in-clinic visit (if the patient has chosen in-clinic visits) or*** ~~is~~ a home visit ***(if the patient has chosen home visits) which will be performed*** by a ~~licensed~~ ***qualified*** person to collect laboratory samples.

Appendix 1, Section 6.5 Central Laboratory Assessment	Serum ***and plasma*** ~~Plasma~~ samples for laboratory analyses will be obtained at 1) Day 0 of the main study; 2) Days 14, 21, 35, 63, 91, and 119 at ***additional clinic visits or*** scheduled ***as*** home visits; 3) ~~At~~ Day 160-178 of the main study. All serum ***and plasma*** laboratory testing ***shall*** ~~will~~ be provided to the ~~unblinded~~ study personnel for review and assessment. ~~Investigators may refer to Appendix 1 for guidance in managing hypophosphatemia.~~ The laboratory assessments will be determined as follows:
Appendix 1, Section 7.2 Reporting of Adverse Events	Please follow guidance ***for reporting of adverse events*** as detailed in the main body of the ***1VIT15043 study*** protocol. ***For qualifying adverse events of hypophosphatemia, the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE Version 5.0) should be followed.*** ***The serum phosphorus level normally ranges from 2.5-4.5 mg/dL or 0.80-1.45 mmol/L in adults. The reporting of hypophosphatemia, per the 2009 NCI CTCAE Version 4.0, is:*** • ***Grade 1: mild (<LLN-2.5 mg/dL; <LLN-0.8 mmol/L),*** • ***Grade 2: moderate (<2.5-2.0 mg/dL; <0.8-0.6 mmol/L),*** • ***Grade 3: severe (<2.0-1.0 mg/dL; <0.6-0.3 mmol/L),*** • ***Grade 4: potentially life threatening (< 1.0 mg/dL; <0.3 mmol/L; life-threatening consequences),*** • ***Grade 5: death. (NCI 2009 [NIH, 2009]).*** ***The updated 2017 NCI CTCAE Version 5.0 includes the revised categorization and reporting of hypophosphatemia to the following:***

	• ***Grade 1: laboratory finding only and intervention not indicated;*** • ***Grade 2: oral replacement therapy indicated;*** • ***Grade 3: severe or medically significant but not immediately life-threatening - hospitalization or prolongation of existing hospitalization indicated;*** • ***Grade 4: life-threatening consequences;*** • ***Grade 5: death. (NCI 2017 [NIH, 2017]).*** ***For this substudy, the analyses of changes in serum phosphate will be captured by laboratory changes, per NCI CTCAE version 4, and/or safety reporting by any interventions determined and reported by the study investigator, per NCI CTCAE version 5.0. Please refer to Table 2: Hypophophosphatemia CTCAE Grade..***
Appendix 1, Section 8.3, Analysis Population	The ~~Hypophosphatemia sub~~ ***sub***-study population will be defined as all participants in the Intent-to-Treat population who provided informed consent to participate in this sub-study. Disposition, demographics, and baseline characteristics will be summarized for the ~~Hypophosphatemia sub~~ ***sub*** -study population. Outcome measurements will be analyzed based on the available data from this population.
Appendix 1, Section 8.4.1, Exploratory Phosphate ***Homeostasis*** Endpoints	The exploratory endpoints will be changes in ***laboratory values*** ~~serum phosphate~~ following ***study drug*** ~~IV iron~~ administration ***for:*** ***1. Serum Phosphorous*** ***2. 1, 25 dihydroxy Vitamin D (1,25[OH]2D)*** ***3. 25 hydroxy Vitamin D (25[OH]D)***

	4. Plasma intact Parathyroid hormone In addition to routine blood chemistry endpoints, the ***above*** ~~following~~ ***laboratory studies*** ~~blood markers of phosphate~~ will be summarized. • ~~Incidence of hypophosphatemia defined as a serum phosphate level <2.0 mg/dL (<0.6 mmol/L)~~ • ~~Serum phosphate levels at each visit and the changes from baseline~~ • ~~1, 25 dihydroxy Vitamin D (1,25 [OH]2D)~~ • ~~25 hydroxy Vitamin D (25OH D)~~ • ~~Plasma intact Parathyroid hormone~~ Details of the analysis of these ***exploratory*** endpoints will be described in the SAP.
Appendix 1, Section 8.5.1, Adverse Events	***Adverse events will analyzed for the sub-study population as detailed in the main body of the 1VIT1503 study protocol.*** ~~Please follow guidance as detailed in the main body of the study protocol.~~
Appendix 1, Section 8.5.2, Clinical Laboratory Tests	The proportion of participants with ~~incident hypophosphatemia (defined as~~ serum phosphate level <***2.5*** ~~2.0~~ mg/dL~~)~~ ***(<0.8 mmol/L), per NCI CTCAE version 4,*** will be summarized by treatment group. Point estimates will be reported with exact two-sided 95% confidence intervals.
Appendix 1, Section 9.1, Informed Consent	The Informed Consent documents the information ***that*** the Investigator provides to the participant ***as well as*** ~~and~~ the participant's agreement to participate. The Investigator will fully explain the nature of the study, along with the aims, methods, anticipated benefits, potential hazards and discomfort that

	participation might entail. The Informed Consent must be signed and dated by each participant before entering the study and prior to the performance of any study specific procedures.
Appendix 1, Section 11, References	***National Institutes of Health (NIH), National Cancer Institute. US Department of Health and Human Services. Common Terminology Criteria For Adverse Events (CTCAE) Version 4.0. Published 2009 May 28 (v4.03: 2010 June 14). Available from: http://evs.nci.nih.gov/ftp 1/CTCAE/CTCAE 4.03 2010-06-14 Quick Reference 5x7.pdf.*** ***National Institutes of Health (NIH), National Cancer Institute. US Department of Health and Human Services. Common Terminology Criteria For Adverse Events (CTCAE) Version 5.0. Published 2017 November 27. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/*** ~~Prinsloo P. Guideline for the treatment of hypophosphataemia in adults by Nottingham University Hospitals, published in March 2016.~~ ~~Zoller H, Schaefer B, Glodny B. Iron-induced hypophosphatemia: an emerging complication. Curr Opin Nephrol Hypertens. 2017;26:266-275.~~
~~Appendix 1, Guidance for Managing Hypophosphatemia~~	~~**Appendix 1 Guidance for Managing Hypophosphatemia**~~ • ~~If serum phosphate is lower than the lower limit of normal (LLN) but > 1 g/dL and asymptomatic, it is acceptable to simply monitor the serum phosphate level~~ • ~~If phosphorus is lower than LLN but > 1 g/dL and accompanied by symptoms associated with hypophosphatemia (e.g., palpitations, dizziness, or muscle weakness) whether or not they are clearly due to hypophosphatemia, the patient may be treated by either the investigator if he/she feels comfortable or in an~~

	~~emergency department if he/she does not feel comfortable treating. Treatment options include dietary sources of phosphate (e.g., dairy products) or oral phosphate supplements~~ • ~~If patient serum phosphate is < 1 g/dL without symptoms, oral phosphate repletion is acceptable at discretion of treating physician.~~ • ~~If patient has phosphate < 1 g/dL and is symptomatic (which may include palpitations, dizziness or muscle weakness, etc.) whether or not they are clearly due to hypophosphatemia, the patient should be evaluated and treated in an emergency department.~~
Table 2.Hypophosphatemia CTCAE Grade	~~See below~~

Table 1 Hypophosphatemia CTCAE Grade

Hypophosphatemia: A disorder characterized by laboratory test results that indicate a low concentration of phosphates in the blood.					
CTCAE Grade:	***Grade 1***	***Grade 2***	***Grade 3***	***Grade 4***	***Grade 5***
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.*	***Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.***	***Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.***	***Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.***	***Life-threatening consequences; urgent intervention indicated.***	***Death related to AE.***
From CTCAE v4.0 Metabolism and Nutrition Disorders - Hypophosphatemia: May 28, 2009: Page 45	***<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L***	***<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L***	***<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L***	***<1.0 mg/dL; <0.3 mmol/L; Life-threatening consequences***	***Death***
From CTCAE v5.0 Metabolism and Nutrition Disorders - Hypophosphatemia: November 27, 2017: Page 94	***Laboratory finding only and intervention not indicated***	***Oral replacement therapy indicated***	***Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated***	***Life-threatening consequences***	***Death***

****A semi-colon indicates 'or' within the description of the grade.***

APPENDIX 1

AMERICAN REGENT, INCORPORATED

PROTOCOL NO. 1VIT15043

IND# 127910

A SUB-STUDY TO CHARACTERIZE SERUM PHOSPHORUS LEVELS OVER TIME WITH INTRAVENOUS FERRIC CARBOXYMALTOSE (FCM) VS. PLACEBO AS TREATMENT FOR HEART FAILURE WITH IRON DEFICIENCY

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For study-related questions, please contact:

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LIST OF ABBREVIATIONS

ALT	Alanine Aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Event
dL	Deciliter
e.g.	for example
FCM	Ferric Carboxymaltose
Fe	Iron
FGF-23	Fibroblast growth factor 23
g	Gram
GGT	Gamma-glutamyl transferase
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDA	Iron Deficiency Anemia
i.e.	that is
IV	Intravenous
Kg	Kilogram
L	Liter
LDH	Lactic dehydrogenase
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mL	Milliliter
N	Number
NCI	National Cancer Institute
PCS	Potentially clinically significant
SAP	Statistical Analysis Plan
SOC	System organ class
U.S.	United States
vs.	Versus
w/v	weight / volume

1. INTRODUCTION

Ferric Carboxymaltose (FCM) is a parenteral form of iron that can be used to treat iron deficiency (IDA) when oral iron is either ineffective or contraindicated [Lyseng-Williamson, 2009]. Several randomized controlled trials demonstrated the efficacy and safety of intravenous (IV) FCM for treating iron deficiency associated with chronic kidney disease, inflammatory bowel disease, heavy uterine bleeding, and during the postpartum period [Barish, 2012; Breymann, 2008; Evstatiev, 2011; Kulnigg, 2008; Qunibi, 2011; Seid, 2008; Van Wyck , 2007; Van Wyck, 2009;Charytan, 2012]. In these populations, several patients who received FCM developed transient and asymptomatic reductions in serum phosphate that typically appeared within 2 to 4 weeks of treatment and resolved spontaneously within 6 to 12 weeks [Van Wyck, 2009].

1.1. Pathophysiology

Phosphate is the most abundant intracellular anion and is essential for membrane structure, energy storage, and transport in all cells. Approximately 85% of the body's phosphorus is in bone as hydroxyapatite, while most of the remainder (15%) is present in soft tissue. Only 0.1 % of phosphorus is present in extracellular fluid and it is this fraction that is measured with a serum phosphorus level [Moe, 2008]. Phosphorus homeostasis is complex and is regulated by several hormones. Hypophosphatemia can occur in the presence of low, normal, or high total body phosphate. In the latter two instances, a shift from the extracellular pool into the intracellular compartment is a major contributory factor. Parathyroid hormone causes phosphate to be released from bone and inhibits renal reabsorption of phosphate, resulting in phosphaturia. Vitamin D aids in the intestinal absorption of phosphate. Thyroid hormone and growth hormone act to increase renal reabsorption of phosphate. Finally, a new class of phosphate-regulating factors, the so-called phosphatonins, including fibroblast growth factor 23 (FGF23), have been shown to be important in phosphate-wasting diseases, such as oncogenic osteomalacia, X-linked and autosomal dominant hypophosphatemic rickets, autosomal recessive hypophosphatemia, and tumoral calcinosis [Shaikh, 2008]. Additionally, FGF23 is up-regulated in patients with early-stage chronic kidney disease to prevent hyperphosphatemia [Takeda, 2011]. A link between IV iron application and increase in FGF23 has been proposed [Takeda, 2011; Schouten, 2009a].

Serum phosphorus concentration is determined by several factors. Dietary phosphorus intake, stage of growth and time of day contribute to the variability of fasting serum phosphorus concentrations. Optimal cellular function is dependent on maintenance of a normal serum phosphorus concentration. The most important determinant of serum phosphorus concentration is regulation of phosphorus reabsorption by the kidney. The majority of this reabsorption (80%) occurs in the proximal tubule and is mediated by an isoform of the Na-phosphate-cotransporter. Parathyroid hormone, via a variety of intracellular signaling cascades leads to Na-phosphate-IIa internalization and down-regulation, and is the main regulator of renal phosphate reabsorption.

Hypophosphatemia is observed in approximately 2% of hospitalized patients, and can be related to decreased intestinal absorption of phosphorus, re-distribution of phosphorus from the extracellular to the intracellular compartment, increased loss of phosphorus through the kidneys, or any combination of these processes. The most common manifestation of hypophosphatemia in hospitalized patients is secondary to re-distribution of phosphorus as a result of respiratory

alkalosis [Amanzadeh, 2006]. Hypophosphatemia has been implicated as a cause of rhabdomyolysis, respiratory failure, hemolysis and left ventricular dysfunction. With the exception of ventilated patients, there is little evidence that moderate hypophosphatemia has significant clinical consequences in humans, and aggressive IV phosphate replacement is unnecessary.

The data on the incidence of hypophosphatemia (defined as <0.64 mmol/L) in outpatients is sparse, but has been reported as 0.9% [Betro, 1972].

1.2. Increased FGF23

Studies have shown that IV FCM, iron polymaltose and saccharated ferric oxide increase the levels of FGF23 post-infusion [Takeda, 2001; Schouten, 2009b; Wolf, 2013]. This hormone, besides the parathyroid hormone, is key for serum phosphate regulation. The phosphatonin FGF23 has been shown to decrease serum phosphate levels by reducing the number of Na-phosphate-cotransporters in the proximal tubule and by inhibiting the production of the active form of Vitamin D [Razzaque, 2007]. FGF23 is predominantly expressed in bone osteocytes [Liu, 2006]. Increased concentrations of circulating FGF23 are central to the pathogenesis of several hypophosphatemic diseases including autosomal-dominant, -recessive, and X-linked hypophosphatemic rickets, tumor-induced osteomalacia and selected cases of McCune-Albright syndrome [Imel, 2005; Yamamoto, 2005].

A study tested the association of IDA with cFGF23 (the C-terminal form of the protein) and iFGF23 (only the intact and hence active form) levels in 55 women with a history of heavy uterine bleeding, and assessed the longitudinal biochemical response over 35 days to equivalent doses of randomly assigned, IV elemental iron in the form of FCM or iron dextran [Wolf, 2013]. The IDA was associated with markedly elevated cFGF23 (807.8± 123.9 RU/mL) but normal iFGF23 (28.5± I. I pg/mL) levels at baseline. Within 24 hours of iron administration, cFGF23 levels decreased by approximately 80% in both groups. In contrast, iFGF23 transiently increased in the FCM group alone, and was followed by a transient, asymptomatic reduction in serum phosphate <2.0 mg P/dL in 10 women in the FCM group compared to none in the iron dextran group. Reduced serum phosphate was accompanied by increased urinary fractional excretion of phosphate, decreased calcitriol levels and increased parathyroid hormone levels. These finding suggest the IDA increases cFGF23 levels, and that certain iron preparations temporarily increase iFGF23 levels. It may therefore be concluded that IV iron lowers cFGF23 in humans by reducing FGF23 transcription as it does in mice, whereas carbohydrate moieties in certain iron preparations may simultaneously inhibit FGF23 degradation in osteocytes leading to transient increases in iFGF23 and reduced serum phosphate. Overall, it seems plausible that an increase in iFGF23 with all the downstream effects may be induced by application of IV iron.

1.3. Inhibition of Vitamin D Activation

It has been described that IV iron might have an inhibitory effect on renal 25-(OH)-Vitamin D Iα-hydroxylase expression [Sato, 1997]. This in turn reduces the availability of 1,25-$(OH)_2$-Vitamin D_3, which leads to decreased absorption of phosphate from the gut and to decreased reabsorption of filtered phosphate in the proximal tubules of the kidney [Sato, 1997]. However, this mechanism was proposed before FGF23 was found to be a direct inhibitor of Iα-hydroxylase expression and it can be assumed that the effect of IV iron on Iα-hydroxylase expression is

triggered via an increase in FGF23 concentration (as mentioned above), which leads to decreased production and increased degradation of 25-(OH)-Vitamin D Iα-hydroxylase [Shimada, 2011; Shimada, 2004a; Shimada, 2004b].

1.4. Symptoms and Signs of Hypophosphatemia

Although an FGF23-mediated decrease in serum phosphate after a single infusion of iron is usually transient, the risk of developing clinical symptoms and the actual clinical presentation is determined by the severity of hypophosphatemia and the time to recovery. Management of hypophosphatemia is within the judgment and discretion of the investigator.

Patients with hypophosphatemia typically report bone pain, general weakness, and asthenia [Okada, 1982;Schouten, 2009b; Mani, 2010; Shiraki, 1986; Sato, 1998; Suzuki, 1998; Konjiki, 1994; Shimizu, 2009; Yamamoto, 2013; Moore, 2013; Blazevic, 2014; Fierz, 2014; Vandemergel, 2014; Barea Mendoza, 2014; Poursac, 2015; Sangros Sahun, 2016]. In severe cases, proximal myopathy that also affects the diaphragm and rhabdomyolysis have been reported. The latter can also affect the heart or cause cardiomyopathy or cardiac arrhythmias [Bacchetta, 2012]. Rare manifestations include hemolysis, encephalopathy, seizures [Haglin, 2016]. The type of clinical manifestation expression is also dependent on the age at onset and the duration of hypophosphatemia. Young patients with long-standing hypophosphatemia typically present with growth retardation, delayed dentation and rickets [Elder, 2014]. In adults with hypophosphatemia persisting for several months, long-term complications such as osteomalacia can occur (Fig.2) [Gonciulea, 2017]. Presentation of osteomalacia can include bone pain, fractures, and pseudofractures, which may be difficult to diagnose on conventional X-ray.

Radiological findings are a coarse trabecular structure, and a loss of secondary trabeculae [Phan, 2016]. Low trauma fractures affecting the ribs or scapular “stress-“ fractures of the lumbar spine, pelvic structures, and long bones such as femur, tibia, or metatarsal are also common complications of osteomalacia. More sensitive diagnostic tests to identify looser zones, known as 'pseudofractures,' include computed tomography, magnetic resonance imaging, and bone scintigraphy. Bone biopsy showing increased ratio of osteoid to bone surface and reduced tetracycline labeling remains the gold standard for diagnosis, but is rarely performed due to its invasiveness. Although there is no specific laboratory test for osteomalacia, mildly elevated total and bone-specific alkaline phosphatase in plasma have been repeatedly reported in the context of iron-induced hypophosphatemia [Phan, 2016].

2. SUB-STUDY OBJECTIVE

The objective of this sub-study is to characterize serum phosphorus levels over time in participants with heart failure with iron deficiency after dosing with FCM versus placebo.

3. SUB-STUDY RATIONALE AND DESIGN

3.1. Sub-Study Rationale

In two randomized clinical studies conducted with FCM (1VIT09030 and 1VIT09031), hypophosphatemia was an adverse drug reaction (treatment emergent adverse event assessed as

related by the Investigator) that occurred in 2.1% (37/1775) of the study participants. Transient decreases in laboratory blood phosphorus levels (< 2 mg/dL) were observed in 27% (440/1638) of participants. Mean decreases from baseline in phosphorus occurred by Day 7, were highest at Day 14 and were returning toward baseline at Day 35 (1VIT09031) or Day 56 (1VIT09030). The objective of this sub-study is to characterize serum phosphorus levels over time in participants with heart failure with iron deficiency after dosing with FCM versus placebo.

3.2. Sub-Study Design

Participation in the sub-study is optional. Although all investigational sites are encouraged to participate, each study site's participation will be determined based on the feasibility of the site to participate. If a site decides to participate, all subsequent participants at the sites will be invited to enroll in the sub-study until enrollment of 110 study participants is achieved. Sites and participants have the option to perform sub-study visits either at the clinic or at a home visit.

A total of approximately 110 participants will be enrolled and the sample size has been determined based on the feasibility of enrollment. Sub-study duration will be up to 6 months for each participant. With this number of participants to be enrolled in the sub-study and the current knowledge on the course of hypophosphatemia with FCM, the evaluation after the initial dosing regimen only was determined to be sufficient to characterize the course of hypophosphatemia in participants with congestive heart failure. A separate informed consent form (ICF) for the sub-study will be signed by participants. Each participant in the sub-study will have additional blood samples collected at either clinic visits or at home visits on Days 14 ± 3, 21 ± 3, 35 ± 3, 63 ± 3, 91 ± 3, and 119± 3). These samples are in addition to the baseline (Day 0) and 6 month (Day 160-176) blood samples collected at the clinic visits for the main study.

3.3. Schedule of Events for Sub-Study

Table 1. Schedule of Events for Sub-Study

	Screening	Treatment Phase		Follow-up Phase							
Visit **Week of main-study**	**-28 to -1**	**Day 0**	**Day 7±2 1**	**Day 14±3* 2**	**Day 21±3* 3**	**Day 35±3* 5**	**Day 63±3* 9**	**Day 90±14† 13**	**Day 91±3* 13**	**Day 119±3* 17**	**Day 160-176, Day 180, Day 187, EOS**
	Participant follows the main study schedule of events							**Participant follows the main study**			**Participant follows the main study schedule of events**
Check that informed consent was signed at screening or at Day 0				X							
Inclusion/ Exclusion criteria				X							
Complete study activities as outlined in the main study Section 3.3	X							X			X
Serum Chemistry (see Section 6.5)				X	X	X	X		X	X	
1,25 $(OH)_2$ Vitamin D‡				X	X	X	X		X	X	
25 (OH) Vitamin D‡				X	X	X	X		X	X	
Parathyroid Hormone‡				X	X	X	X		X	X	

* In Clinic or Home visit
† Phone call or clinic visit
‡ Reminder that laboratory testing for 1,25 $(OH)_2$ Vitamin D, 1,25 $(OH)_2$ Vitamin D, and Parathyroid Hormone levels are also done outside the hypophosphatemia substudy at Day 0 and Day 160-176

4. PARTICIPANT SELECTION

4.1. Number and Type of Participants

Approximately 110 participants newly enrolled in the main 1VIT15043 study, who fulfill the inclusion criteria, do not meet any of the exclusion criteria and who have given written informed consent will be included.

4.2. Participant Selection

4.2.1. Inclusion Criteria

1. Demonstrate the ability to understand the requirements of the sub-study, willingness to abide by sub-study participation, and to return for the required assessments.

4.2.2. Exclusion Criteria

1. History of primary hypophosphatemic disorder (for example X-linked hypophosphatemia)
2. Baseline serum phosphate <2.5 mg/dL
3. Untreated primary hyperparathyroidism.

4.3. Participant Assignment and Randomization Process

Please follow guidance as detailed in the main body of the protocol.

4.4. Withdrawal from Study

Please follow guidance as detailed in the main body of the protocol.

5. CONCOMITANT MEDICATION

Please follow guidance as detailed in the main body of the protocol.

6. STUDY PROCEDURES

6.1. Treatment Phase

For Day 0 and Day 7 visits, follow guidance as detailed in the main body of the protocol.

6.2. Informed Consent

Check that the participant signed an informed consent form for the hypophosphatemia study at screening or at Day 0.

Prior to any study specific procedures, the investigator or his or her designee must explain to each participant the nature of the study, study purpose, procedures to be performed, expected duration, and the benefits and risks of study participation. After this explanation the participant must voluntarily sign an informed consent statement (Required Elements of Informed Consent, 21 CFR 50.25). The participant will be given a copy of the signed consent form.

6.3. Follow-up Phase

Clinic visits will be performed by study personnel.

Home visits will be performed by a contracted third party person qualified to collect blood or site personnel.

Once a home visit or clinic visit choice has been made, that patient must continue with that venue for the those visits for the duration of their sub-study participation.

After completing the 6-month sub-study, the participant returns to follow the main study protocol.

6.3.1. Sub-study Specific Visit Days 14 ± 3, 21 ± 3, 35 ± 3, 63 ± 3, 91 ± 3, 119 ± 3 (Clinic or Home Visits)

- Laboratory samples will be collected
  - Serum for:
    - Chemistry (see Section 6.5 for details)
    - 1,25 (OH)2 Vitamin D
    - 25 (OH) Vitamin D
  - Plasma for:
    - Parathyroid Hormone

Note that Visit Day 90±14 days (Phone call or Study visit) is a procedure in the main protocol to collect adverse event / serious adverse event assessment, including evaluation of potential endpoint events (blinded staff).

Study Visit Day 91±3 days will be an in-clinic visit (if the patient has chosen in-clinic visits) or a home visit (if the patient has chosen home visits) which will be performed by a qualified person to collect laboratory samples.

6.4. End of Sub-Study

Sub-study visits only occur within the first 180 days. No other sub-study dosing or blood collections will occur after that time.

6.5. Central Laboratory Assessment

Serum and plasma samples for laboratory analyses will be obtained at 1) Day 0 of the main study; 2) Days 14, 21, 35, 63, 91, and 119 at additional clinic visits or scheduled as home visits; 3) Day 160-178 of the main study. All serum and plasma laboratory testing shall be provided to the study personnel for review and assessment. The laboratory assessments will be determined as follows:

Chemistry:	Sodium, potassium, chloride, BUN, creatinine, albumin, alkaline phosphatase, total bilirubin, GGT, AST, ALT, LDH, calcium, phosphate, glucose, bicarbonate and magnesium
Other:	1,25 dihydroxy Vitamin D; 25 hydroxy Vitamin D
Plasma:	Parathyroid Hormone

7. ASSESSMENT OF SAFETY

7.1. Adverse Events

7.2. Reporting of Adverse Events

Please follow guidance for reporting of adverse events as detailed in the main body of the 1VIT15043 study protocol. For qualifying adverse events of hypophosphatemia, the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE Version 5.0) should be followed.

The serum phosphorus level normally ranges from 2.5-4.5 mg/dL or 0.80-1.45 mmol/L in adults. The reporting of hypophosphatemia, per the 2009 NCI CTCAE **Version 4.0**, is:

- Grade 1: mild (<LLN-2.5 mg/dL; <LLN-0.8 mmol/L),
- Grade 2: moderate (<2.5-2.0 mg/dL; <0.8-0.6 mmol/L),
- Grade 3: severe (<2.0-1.0 mg/dL; <0.6-0.3 mmol/L),
- Grade 4: potentially life threatening (<1.0 mg/dL; <0.3mmol/L; life-threatening consequences),
- Grade 5: death. (NCI 2009 [NIH, 2009]).

The updated 2017 NCI CTCAE **Version 5.0** includes the revised categorization and reporting of hypophosphatemia to the following:

- Grade 1: laboratory finding only and intervention not indicated;
- Grade 2: oral replacement therapy indicated;
- Grade 3: severe or medically significant but not immediately life-threatening - hospitalization or prolongation of existing hospitalization indicated;
- Grade 4: life-threatening consequences;
- Grade 5: death. (NCI 2017 [NIH, 2017]).

For this substudy, the analyses of changes in serum phosphate will be captured by laboratory changes, per NCI CTCAE version 4.0, and/ or safety reporting by any interventions determined and reported by the study investigator, per NCI CTCAE version 5.0. Please refer to Table 2: Hypophophosphatemia CTCAE Grade.

8. STATISTICS

Given the exploratory nature of this sub-study, the focus of the analyses will be on estimation rather than hypothesis testing. Continuous variables will be summarized in terms of the number of observations, mean, standard deviation, median, minimum, and maximum. Other descriptive statistics (e.g., quartiles, coefficient of variation) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages. Two-sided 95% confidence intervals will be presented, when appropriate.

Complete details of the analysis for this sub-study will be outlined in a Statistical Analysis Plan (SAP). This SAP will be completed prior to database lock.

8.1. Stratification/Randomization

Please follow guidance as detailed in the main body of the protocol.

8.2. Sample Size Rationale

No formal sample size calculations were made. Sample size for this sub-study was based on feasibility and practicality. The target sample size will be a total of approximately 110 participants, i.e., 55 participants per treatment group.

8.3. Analysis Population

The sub-study population will be defined as all participants in the Intent-to-Treat population who provided informed consent to participate in this sub-study.

Disposition, demographics, and baseline characteristics will be summarized for the sub-study population. Outcome measurements will be analyzed based on the available data from this population.

8.4. Endpoints and Definitions

8.4.1. Exploratory Phosphate Homeostasis Endpoints

The exploratory endpoints will be changes in laboratory values following study drug administration for:

1. Serum Phosphorous
2. 1, 25 dihydroxy Vitamin D (1,25[OH]2D)
3. 25 hydroxy Vitamin D (25[OH]D)
4. Plasma intact Parathyroid hormone

In addition to routine blood chemistry endpoints, the above laboratory studies will be summarized.

Details of the analysis of these exploratory endpoints will be described in the SAP.

8.5. Safety Analyses

8.5.1. Adverse Events

Adverse events will analyzed for the sub-study population as detailed in the main body of the 1VIT15043 study protocol.

8.5.2. Clinical Laboratory Tests

Clinical laboratory data will be summarized by scheduled visit using descriptive statistics. The actual values as well as the change from baseline will be summarized. Unscheduled visits will be excluded from these by-visit summaries. Maximum changes relative to baseline will be over all visits (both scheduled and unscheduled).

The time course for changes in serum phosphate will be evaluated and compared to that of other laboratory parameters.

Where applicable, the number and percent of participants with laboratory values outside pre-determined ranges will be summarized by scheduled visit. Unscheduled visits will be excluded from these by-visit summaries. The number and percent of participants with the laboratory values outside pre-determined ranges at any time during the sub-study will be summarized; and these summaries will be over all visits (both scheduled and unscheduled).

The proportion of participants with serum phosphate level <2.5 mg/dL (<0.8 mmol/L), per NCI CTCAE version 4, will be summarized by treatment group. Point estimates will be reported with exact two-sided 95% confidence intervals.

Full details will be described in the SAP.

9. ETHICS

9.1. Informed Consent

Informed consent must be obtained from each participant prior to sub-study participation. The informed consent will be provided to the participant in their native language. The consent form must be signed by the participant. Each investigational site must provide the Sponsor (or designee) with a copy of the Informed Consent approved by that site's Institutional Review Board. The original signed consent form will be retained in the participant's study records, and a copy will be provided to the participant. The Clinical Monitor will assure that each Informed Consent meets the requirements of Parts 50.20 and 50.25 of Title 21 of the CFR, which outlines the basic elements of informed consent and International Conference on Harmonisation (ICH) guidelines. Translations of the informed consent must be certified by a qualified translator and their use must be documented.

The Informed Consent documents the information that the Investigator provides to the participant as well as the participant's agreement to participate. The Investigator will fully explain the nature of the study, along with the aims, methods, anticipated benefits, potential hazards and discomfort that participation might entail. The Informed Consent must be signed and dated by each participant before entering the study and prior to the performance of any study specific procedures.

9.2. Good Clinical Practice

The conduct of the study will conform with the recommendations for clinical studies in man as set out in the 2000 Edinburgh, Scotland Revision of the "Declaration of Helsinki", the local legal requirements and the guidelines on "Good Clinical Practice", [21 CFR Part 312 and ICH guidelines.

10. DATA HANDLING AND RECORD KEEPING

10.1. Case Report Form

The eCRFs will be completed for each participant on this study. The participants in this study will be identified only by a participant number and date of birth on these forms.

The eCRF used will be 21 CFR 11 compliant. The system used for data collection (eCRF) will meet all applicable regulatory requirements for recordkeeping and record retention as would be provided with a paper system. Security measures will be utilized to prevent unauthorized access to the data and to the computerized system. Changes made to data that are stored on electronic media will always require an audit trail, in accordance with 21 CFR 11.10(e).

The eCRFs must be reviewed and verified for accuracy by the Principal Investigator. An electronic copy of the eCRF will remain at the site at the completion of the study.

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Table 2. Hypophosphatemia CTCAE Grade

Hypophosphatemia: A disorder characterized by laboratory test results that indicate a low concentration of phosphates in the blood.					
CTCAE Grade:	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.*	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.	Life-threatening consequences; urgent intervention indicated.	Death related to AE.
From CTCAE v4.0 Metabolism and Nutrition Disorders - Hypophosphatemia: May 28, 2009: Page 45	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; Life-threatening consequences	Death
From CTCAE v5.0 Metabolism and Nutrition Disorders - Hypophosphatemia: November 27, 2017: Page 94	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences	Death

*A semi-colon indicates 'or' within the description of the grade.

Statistical Analysis Plan

for

Heart Failure with Iron Deficiency (HEART-FID).

Version: 1.0

Date: 21 September 2021

Clinical Study Protocol/Amendment No: 1VIT15043/3

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF INJECTAFER® (FERRIC CARBOXYMALTOSE) AS TREATMENT FOR HEART FAILURE WITH IRON DEFICIENCY.

Prepared by: CT Statistics Group
[Duke Clinical Research Institute]

Prepared For: American Regent, Inc.
[Sponsor]

Statistical Analyses Plan Amendment x

The original Statistical Analysis Plan was finalized and issued on 21/Sep/2021. Major changes and clarifications of planned analyses in SAP Vx.0 since the original SAP are listed below

Version	Date	Author(s)	Brief Summary of Changes
V1.0	21/Sep2021	[redacted]	Final version after American Regent's final comments on 14/Sep/2021. Signed.

TABLE of CONTENTS

LIST OF ABBREVIATIONS

6MWT	6 Minute Walk Test
ADaM	Analysis Data Model
AE	Adverse Experience
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CEC	Clinical Events Committee
CKD	Chronic Kidney Disease
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DCRI	Duke Clinical Research Institute
DSMB	Data and Safety Monitoring Board
EDC	Electronic Data Capture
FCM	Ferric Carboxymaltose
GGT	Gamma-Glutamyl Transferase
Hb	Haemoglobin
Hct	Haematocrit
HF	Heart Failure
HLT	High Level Term
HR	Hazard Ratio
HS	Hypophosphatemia Sub-study
ICH	International Council for Harmonisation
ITT	Intent-To-Treat
IV	Intravenous
IXRS	Interactive Web Response Systems
LDH	Lactate Dehydrogenase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NYHA	New York Heart Association
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cell
RDW	Red Cell Distribution Width

SDTM	Study Data Tabulation Model
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SD	Standard Deviation
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
TESAE	Treatment Emergent Serious Adverse Experiences
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
WBC	White Blood Cell

1 INTRODUCTION

HEART-FID is a double-blind, multicenter, prospective, randomized, placebo-controlled study to assess the effects of intravenous (IV) ferric carboxymaltose (FCM) compared to placebo on the hierarchical, composite endpoint of 12-month rate of death and hospitalization for worsening heart failure and change in 6 minute walk test (6MWT) at 6 months for participants in heart failure with reduced ejection fraction and with iron deficiency. The reader of this Statistical Analysis Plan (SAP) is also encouraged to read the corresponding protocol (1VIT15043, version 3.0, 11 January 2021) which provides detail on the conduct of the study, the operational aspects of clinical assessments, and the timings of individual participant assessments.

This SAP contains definitions of analysis populations, and details on the statistical methods for the analyses and summaries of study data that are to be performed, to help support the completion of the final Clinical Study Report (CSR) for study 1VIT15043. Details regarding analysis of the hypophosphatemia sub-study can be found in a supplemental SAP. Information on important definitions and reporting conventions and table shells to support the SAP will be in a supplemental Appendix.

Specifications of supporting tables, figures, and data listings are contained in a separate document.

Outcomes that are confirmed by clinical events classification (CEC) adjudication, the process for which is governed by specific charters referenced in the protocol, will be referred to as "confirmed" events in the SAP. The term outcome is used throughout this document as synonymous with the term endpoint used in the clinical trial protocol. The following events are confirmed by the CEC in HEART-FID: Death (Cardiovascular [CV] and Non-Cardiovascular), Cardiovascular Hospitalizations (Heart Failure, Acute Myocardial Infarction [MI], Stroke, and Other cardiovascular hospitalizations), and Urgent Heart Failure Visit. CEC data take precedence over investigator data when both are available and investigator response is different from the CEC adjudicated response.

1.1 Study Objectives

1.1.1 Primary Objective

To determine the efficacy and safety of iron therapy using intravenous (IV) FCM, relative to placebo, in the treatment of participants in heart failure with reduced ejection fraction and with iron deficiency.

1.1.2 Secondary Objective

To evaluate the effect of IV FCM, relative to placebo, on the functional capacity of participants in heart failure with reduced ejection fraction and with iron deficiency.

1.2 Study Design

This is a double-blind, multicenter, prospective, randomized, placebo-controlled study to assess the effects of IV FCM compared to placebo on the 12-month rate of death, hospitalization for worsening heart failure, and change in 6MWT from baseline at 6 months for participants with heart failure, reduced ejection fraction, and with iron deficiency.

After an initial screening period of up to 28 days, eligible participants will be stratified by region and randomized in a 1:1 ratio to FCM or placebo. Study drug administration will occur on Day 0 and Day 7 as an undiluted slow IV push, with additional study visits (in person or via telephone) planned at 3 month intervals, and additional dosing administered every 6 months as applicable (based on dose regimen below).
For all participants, laboratory tests for haematology, ferritin, and transferrin saturation (TSAT) with appropriate safety evaluations, to determine additional treatment, will occur at 6 month intervals.

In a subset of sites, a sub-study will be conducted to characterize serum phosphate levels over time in participants in heart failure with reduced ejection fraction with iron deficiency after dosing with FCM. There will be additional visits for these participants during the first 6 months (Clinical Study Protocol [CSP] Appendix 1, Section 3.3)

Initial treatment will occur on Day 0 and Day 7. On Day 0 and 7, Group A (FCM) will receive a 750 mg undiluted, blinded dose of IV FCM at the rate of approximately 100 mg (2 mL)/minute (approximately 7 minutes 30 seconds); Group B (placebo) will receive a blinded placebo (15 cc of normal saline) IV push at 2 mL/minute (approximately 7 minutes 30 seconds). Participants in Group A with body weight <50 kg (110 pounds) will have individual FCM doses adjusted to 15 mg/kg, not to exceed an individual dose of 750 mgs or a cumulative dose of 1500 mg per treatment cycle. Placebo dosing will be adjusted for weight based on volume.

All participants randomized will be dosed every 6 months. Participants randomized to the FCM arm will be dosed as indicated based on haemoglobin levels (i.e. Hb <13.5 g/dl [females] or <15.0 g/dl [males)]) and iron studies (i.e. serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%). Participants not meeting pre-specified laboratory criteria for blood counts and iron studies and all participants randomized to the placebo arm will be administered IV placebo infusion at each visit.

Unblinded site personnel, responsible for preparation and administration of the FCM or Placebo, will ensure that the participant and all blinded site staff are not able to observe the preparation or administration of study treatment.

1.3 Randomization and Blinding

The randomization scheme was generated by a statistician at DCRI who is firewalled to the operational team, using Statistical Analysis System (SAS) with region as the only stratification field. Blocking was used in the scheme with random block sizes (3 different levels). This scheme was implemented into the Interactive Web Response Systems (IXRS) by the vendor Almac. The vendor maintains randomized treatment assignments as well as unblinded kit dispensation information. The operational team for this trial is to remain blinded until data base lock, at which time the unblinded treatment codes received from Almac will be combined with blinded data.
In the event of the need to break an individual participant blind, the site can call Almac for this information. The operational team gets informed if such unblinding occurs; however, they do not know the true treatment assignment.
The 3 regions are defined within the randomization scheme as follows (Details can be found in the SAP Appendix for Definitions and Reporting Conventions):

- North America
- Asia Pacific
- Europe

1.4 Sample Size and Power

The study design allows for sufficient power for both the primary and top secondary outcomes. Numerical simulations based on multivariate normal vectors (Appendix 2) were conducted to estimate power for the primary treatment comparison based on the following assumptions about events rates described in **Table 1.4.1**

Table 1.4.1. Assumptions about Event Rates for Primary Outcome

Ranked tier at 12-month endpoint (6 month for 6 MWT)	Control	Treatment
Death total **Death without hospitalization** **Death with hospitalization**	8% 4% 4%	6.8% 3.4% 3.4%
Hospitalizations in survivors **1** **2** **3 or more**	 6% 3% 1%	 4.8% 2.4% 0.8%
Change in 6 Minute Walk Test	Mean = 0 SD = 90	Mean = 18 SD = 90

With 3014 participants (1507 per arm) and 2.5% annual loss to follow-up for clinical outcomes and 15% of individuals with missing 6MWT at 6 months (unable to perform or lost to follow-up), projected simulations estimate 90% power at an overall two-sided significance level of 0.01, accounting for one interim analysis as described in Section 7.1.

For the top secondary composite, there is an assumed event rate of 0.0128 per month in the control arm which represents conservative 75% discounting of the event rate obtained by the FCM meta-analysis [Anker 2015]. The anticipated hazard ratio (HR) was set at 0.80 (20% reduction). Uniform enrollment was assumed over the period of 30 months, with an anticipated minimum follow-up of 12 months (required minimum of 6 months), anticipated maximum follow-up of 42 months (no required maximum), and monthly loss to follow-up of 0.0021 (2.5% annualized). With these assumptions, 1500 per study arm (3000 total) provides 90% power to reject the null hypothesis of no difference between treatment arms when tested at an overall two-sided level of significance α=0.05, accounting for one interim analysis as described in Section 8.10. This results in a total of 771 participants with events (in case of multiple events experienced by a participant, only their first one will be counted towards the 771) necessary to achieve the desired power. Thus, the trial has the potential opportunity to be stopped at a point where the projected number of participants reaches 771 events, but no earlier than the last participant reaching 12 months of follow-up.
The primary and top secondary outcome will be tested sequentially, and thus, no multiplicity adjustment is necessary.

1.5 Schedule of Major Assessments

Following randomization, outcomes and serious adverse event data are collected at 90 days and at every 6 monthly visit as detailed in schedule of events (Section 3.3 of the CSP)

1.6 Summary of Relevant Amendments to the Protocol

Please refer to Appendix 1 for this information. The version the participant was enrolled under will be available in the database.

2 ANALYSIS SETS

2.1 Intent-to-treat (ITT) Population

The ITT population consists of all participants randomized to a treatment group in the study regardless of their compliance with the study medication. The participants are analysed in the

treatment group to which they were randomized. This is the primary population of all efficacy analyses.
Any participant who gets a treatment assigned via the IXRS will be considered to have been randomized.

2.2 Safety Population

The Safety population will consist of all ITT participants who received at least 1 dose of study medication identified by the presence of injection start date. When summarizing data using this population, participants are analyzed in the As Treated group. If a participant receives any FCM study drug, then the participant will be counted as treated in the FCM arm, regardless of the amount of medication received; otherwise the participant will be counted as treated in the placebo arm.
The Safety population will be used for assessing Safety.

2.3 Per-protocol (PP) Population

The Per-Protocol Population is a subset of the ITT population excluding participants who complied with the randomized treatment for less than 50% of the 1 year follow-up. In cases of medication error, treatment assignments in the per-protocol analysis will be analyzed according to the actual treatment received as the first study drug dose.

2.4 Hypophosphatemia Sub-study (HS) Population

The Hypophosphatemia Sub-study (HS) population will consist of all ITT participants who enrolled in the sub-study identified by the presence of injection start date. When summarizing data using this population, participants will be analyzed according to the actual treatment received as the first dose.
The HS population will be used for assessing Safety.
Please see the HS SAP for further details.

3 BACKGROUND CHARACTERISTICS

3.1 Disposition of Participants

Disposition data will be summarized for all randomized participants. The summary by treatment will include

- Inclusion in the three study populations
- Participants completing study alive
- Lost to follow up
- Withdrawn consent for follow up
- Reason study drug permanently discontinued

3.2 Demographic and Baseline Characteristics

The demographic, baseline clinical and anthropometric characteristics collected in the study will be tabulated and summarised as descriptive statistics by treatment for both ITT and Safety populations.

3.3 Medical History

Participant medical history will be summarized within both ITT and Safety populations.

- Duration of heart failure calculated as (year of randomization – year of onset) +1 and etiology of heart failure at baseline will be summarized by treatment.

All other medical history data collected in the study will be summarized by treatment group.

4 METHODS OF ANALYSIS

4.1 General Principles

In addition to specific analyses and presentations that are detailed in the following sections, results will be summarised using descriptive statistics, including the number of participants, mean, standard deviation, median, and range as appropriate. For categorical variables, counts and percentage per treatment group will be presented.

Summaries of continuous characteristics will be based on non-missing observations. Percentage for categorical variables will be calculated based on number of participants with non-missing values for the variable.

Unless otherwise stated, timings of efficacy endpoints will be relative to the date of randomization. Specifically, for all time-to event analyses (defined as [event date – randomization date] +1 where event occurs and as [appropriate censoring date based on analytic population – randomization date] +1 where event does not occur), the treatment groups will be analysed using a Cox proportional hazards model that includes treatment as an explanatory factor and region as stratification factors unless specified otherwise. The Efron method will be used for handling ties. P-value and confidence intervals for the HR will be based on the Wald statistic. Any analyses using events that are confirmed by the CEC will use the CEC adjudicated responses and related dates. Analyses of Cardiovascular (CV) death, will include deaths with cause of death confirmed as unknown.
In addition, the summary tables of these analyses will include the number of participants with event and the cumulative incidence (1 – the "survival" or event-free proportion) over time per treatment group presented annually through the last time point where 90 % of the events have occurred. Cumulative incidence function of participants with events will also be calculated and plotted through maximum follow up available in the study, with number of participants at risk indicated below the plot at specific times.
The timing of safety data will be relative to the study drug start date. Specifically, any time to safety event durations will be defined as [event date – study drug start date] +1 where event occurs and as [appropriate censoring date based on analytic population – study drug start date] +1 where event does not occur).
Baseline is defined as response/value collected closest to randomization date and prior to study drug start.
Date of last follow-up for the participant will be driven off of the date of their final study disposition. This can be different from date of mortality status for lost to follow-up or withdrawn consent participants.
The median and total person-years of follow-up for the whole study will also be reported.

All analyses included in this SAP will be performed using SAS v9.4 or higher. They will be based on Clinical Data Interchange Standards Consortium (CDISC) standard data (Analysis Data Model (ADaM) and/or Study Data Tabulation Model (SDTM)). The summaries will be presented as either tables or, where appropriate, as figures. International Council for Harmonisation (ICH) required listings will also be produced.

- "n" will be displayed as a whole number
- The Mean, SD, Median, Q1, and Q3 will be displayed with 1 more decimal place than the source data precision.

- The Min and Max will be displayed with the same number of decimal places as the source data. Any other presentation of raw data will be also be displayed with the same decimal places as the source data.

- All tests and confidence intervals are 2-sided unless specified otherwise.

- All p-values will be displayed with three decimal places.

- All by visit summaries and analyses will use analyses visits. Analysis visits will be derived from the date of assessment (or visit date if assessment date is not collected or is missing) relative to randomization date. Visit windows will be contiguous (Details will be included in the SAP Appendix for Definitions and Reporting Conventions)

4.2 Multiple comparisons

We will complete multiplicity adjustment as noted in the CSP Section 8.8. The primary and top secondary outcomes will be tested sequentially, and thus, no multiplicity adjustment is necessary

4.3 Visit Windows for Analysis

Visit windows for presentation of results will be derived from date of the assessment (or visit date if assessment date was not collected or is missing). Visit windows will be contiguous and are based on assessment-specific scheduled visits. The specific windows for the study are included in the Appendix for definitions.

4.4 Right Censoring

In this study we expect missing outcome data to be infrequent and every effort will be made to collect all information regarding the primary outcomes prior to study termination, even in those who have discontinued the study treatment.

In primary and secondary analyses in the ITT population, the observation time for participants who have not had an event in the analysis of a specific outcome will be right censored at the date of last contact where all elements of the outcome could be assessed. Same algorithm will be followed for inclusion of events in the analyses.

Note that for the analysis of the components of the primary composite outcome, participant exposure will be censored at the date of the occurrence of the component outcome of interest.

Note that for outcomes not including CV death, all deaths are censoring events.

Participants that withdraw consent for follow-up or are lost to follow-up at the end of study will be censored at the last contact where all elements of the outcome could be assessed.

In safety time-to-event analyses in the Safety population, participants who have not had the event in question will be censored following same rules as detailed for the ITT population.

4.5 Handling of Missing Data

4.5.1 Outcome Data/Dates

The primary analysis will rely on a multiple imputation model, with Markov chain Monte Carlo algorithm based on the totality of observed data. One exception to this rule will be that individuals unable to perform the 6MWT test at 6 months will have their value imputed as the worst observed change in 6MWT.

The SAS PROC MI procedure will be used for multiple imputations, with 20 imputations on each variable. To ensure consistency in the imputed data for future possible validations, a seed number will be fixed to 1000 for every study variable. Imputed data set(s) will include an index variable to identify the number of imputed data. The results across the imputed datasets will be combined using Rubin's rule (Rubin 1987) to obtain one set of results for a given variable. Basic statistics

on the original data (incomplete data) and the data following imputation for each of the relevant study variable will be provided in the Clinical Study Report (CSR).

For secondary efficacy endpoints, missing data relating to the indicator for the confirmed composite CV outcome and/or its components will not be imputed. Any partial or completely missing date for a confirmed composite CV outcome at the time of database lock will be imputed as follows:

- If the day is missing, 15th of the month, or the randomization date (if participant randomized after 15th of the same month and same year) will be used, making sure the imputed date is not post end of study date;
- If the month is missing, June, or the randomization month (if participant randomized after June and year of the event is same as randomization year) will be used, making sure the imputed date is not post end of study date;
- If the complete date is missing, the midpoint between randomization and the date of last known event-free visit will be used.

4.5.2 Other Missing Data

Any other partial date of relevance (for example, date of last study contact at the time of database lock will be imputed as follows:

- If the day is missing, 15th of the month, or the randomization date (if participant randomized after 15th of the same month and same year) will be used, making sure the imputed date is not post end of study date.
- If the month is missing, June, or the randomization month (if participant randomized after June and year of the event is same as randomization year) will be used, making sure the imputed date is not post end of study date.

We do not plan to impute any missing baseline data.

4.6 Assessment of Model Assumption

The validity of the proportional hazards assumption made in the secondary analysis will be examined using standard graphical methods such as Log (-log) plots; if the assumption holds the curves should be approximately parallel to each other.

An additional analytical method that includes treatment*log (time) as a factor in the model and tests the interaction factor at the 0.05 significance level may be employed; non-significance ($p>0.05$) of this factor would suggest proportionality.

If there is evidence of non-proportionality its cause will be investigated by exploring hazard ratios within few pre-specified clinically meaningful time landmarks such as every six months.

5 OUTCOMES

Please refer to Section 10.2 of the CSP for information on which endpoints are adjudicated.

5.1 Primary Outcome

The primary outcome follows an ordinal scale of clinical severity comprised of 1) confirmed death, 2) number of confirmed hospitalizations for heart failure evaluated at one year; or 3) change in 6MWT from baseline evaluated at 6 months.

Each participant from the treatment arm gets ranked/compared with each participant from the control arm based on the 12-month experience for Death and Hospitalizations for heart failure

and 6 month results for change in 6MWT to determine treatment response per the following hierarchy:

1. Death

If both die, the one who survives longer is better off;
If one dies and one does not, the one that survives is better off;
If neither dies, examine hospitalizations for heart failure.

2. Hospitalizations for heart failure

The one with fewer hospitalizations is better off;
If neither has been hospitalized for heart failure or the number heart failure hospitalizations is equal, compare change in 6MWT.

3. Change in 6MWT

The one with higher change in 6MWT is better off;

5.2 Top Secondary Outcome

The top secondary outcome is defined as the time from randomization to the onset of first confirmed event in the composite CV outcome of CV-related death (any deaths confirmed as unknown are included in CV deaths) or hospitalization for heart failure.

In the unlikely event that two confirmed outcomes occur on the same day, the following hierarchy will be used to ascribe the primary component of the composite:

- CV-related death
- Hospitalization for heart failure

5.3 Analyses of the Primary and the Top Secondary Outcome

The analytic approaches for the primary and top secondary outcome are detailed in below sections.

5.3.1 Nonparametric Test of FCM vs. Placebo for Primary Composite

The null hypothesis being tested is that a randomly chosen participant in the treatment arm is equally likely to be ranked better or worse than a randomly chosen participant in the control group. The two-sided alternative is that the participant is not equally likely to be ranked better or worse.

In addition to performing the test, we will estimate the probability that a participant in the treatment arm has a better rank than a participant in the control arm and its corresponding confidence interval.

The main comparison will be conducted using the Wilcoxon-Mann-Whitney test in ITT population relying on multiple imputation model as summarized in Section 4.5.1.

The above comparison of participants in the treatment versus control arms is equivalent to ranking all participants according to their experience. At one end of the ranking are participants with the best experience - those alive and not hospitalized for worsening heart failure ordered according to their improvement in 6MWT; at the opposite end are those who die ordered according to their survival time. Those participants alive but hospitalized are in the middle, ordered according to their number of hospitalizations for worsening heart failure and then by their change in 6MWT. The non-parametric Wilcoxon-Mann-Whitney test sums the ranks of those in the treatment arm and compares them with the sum of ranks in the control arm (Finklestein 1999).

In all analyses, the number of hospitalizations (and the number of days in the hospital in the sensitivity analysis described in Section 5.3.1.1) will be adjusted for the time in follow-up. This adjustment applies only to individuals who are alive at the end of follow-up (the comparison in those who die will be resolved based on time to death) and will be accomplished by dividing the observed number by time at risk in years. For individuals who complete the pre-specified 12 months of follow-up, time at risk equals 1. For all others, it is equal to the fraction of 12 months that the person remained in the study.

5.3.1.1 Sensitivity Analysis (Additional Layer to Hierarchy) for Nonparametric Test of FCM vs. Placebo for Primary Composite

In a sensitivity analysis we will add another layer to the hierarchy described above – in individuals who have been hospitalized for heart failure during follow-up, ties in the numbers of hospitalizations will be resolved based on the total number of days in the hospital during follow-up, before proceeding to comparison of differences in the 6MWT. This will be conducted in the ITT population only.

5.3.1.2 Sensitivity Analysis for Potential Covid-19 Impact for Nonparametric Test of FCM vs. Placebo for Primary Composite

In case there are 5% or more of randomized participants with missing 6 month 6MWT due to COVID-19 who also did not have a qualifying clinical event (death or heart failure hospitalization through 1 year), then we will assess the sensitivity of primary results to the missing data by conducting a tipping point analyses on the primary analyses method in ITT population.
The tipping point analysis will assume progressively biased tie breaking. Hence, starting with all missing 6MWT values favouring the placebo to break the tie and checking if this does not change inference from the primary analyses. However, if it does change the inference then we will continue going down the scale to find the tipping point.

5.3.1.3 Key Supportive Analysis for Nonparametric Test of FCM vs. Placebo for Primary Composite

As the key supportive analysis, the null hypothesis for the primary composite end point, that a randomly chosen participant in the treatment arm is equally likely to be ranked better or worse than a randomly chosen participant in the control group, will be tested using the same approach as in the primary analysis based on PP population.

In case of a difference in inference between the primary analysis and the key supportive analyses, further exploratory analyses will be conducted to understand the reason for a possible difference.

5.3.1.4 Supportive Analysis (Impute to Worst Observed Change) for Nonparametric Test of FCM vs. Placebo for Primary Composite

We will use multiple imputation for clinical outcomes in the primary composite, but will impute the worst observed change in 6MWT to all individuals who do not have this measurement, regardless of the reason. This will be conducted in the ITT population only.

5.3.1.5 Supportive Analysis (Tipping Point) for Nonparametric Test of FCM vs. Placebo for Primary Composite

We will perform tipping point assessments to determine the sensitivity of the observed result to the missing data. Given the multi-dimensional nature of outcomes, tipping point analyses will be performed separately for each outcome: mortality, hospitalization for heart failure, and 6MWT. This will be conducted in the ITT population only.

5.3.1.6 Supportive Analysis (Total burden of HF impact) for Nonparametric Test of FCM vs. Placebo for Primary Composite

To further understand the burden of the disease, we will analyse a combined endpoint of CV death and frequency of intervention for worsening heart failure (hospitalization or urgent heart failure

visits), through the duration of the study. The analytic methods will follow that for the primary analyses. The analysis will be conducted in the ITT population only.

5.3.2 FCM vs. Placebo for Top Secondary Outcome

This analysis will compare time from randomization to the first occurrence of CV death or hospitalization for heart failure. The Cox proportional hazards model will be employed to conduct this comparison. The cox model will be adjusted for baseline covariates decided prior to database lock. The test will be two-tailed and will be performed at an overall α of 0.05. This analysis will be performed by the ITT principle based on randomized treatment assignment and we expect adequate power to detect a pre-specified relative risk reduction of 20%.

5.3.2.1 Supportive Analysis for FCM vs. Placebo for Top Secondary Outcome

As supportive analysis, time from randomization to the first occurrence of CV death or hospitalization for heart failure will be analysed in PP using the same approach as for the primary analysis based on the ITT population.

5.4 Subgroup Analyses for Top Secondary Outcome

Subgroup analyses will be performed for the top secondary outcome in the ITT population in order to explore whether treatment effects on the risk of developing CV events are consistent across subgroups. Subgroup analyses will be performed using the same analysis models as for the top secondary endpoints, with the addition of the subgroup factor and its interaction with treatment. The same subgroup analyses will also be repeated in the PP population.

The subgroups will be divided by categories for continuous variables. The subgroup analyses will be summarized via a forest plot and interaction p-values will be reported.
Pre-specified subgroups are detailed below.

Key Subgroups of Interest include split by:
Age, BNP, NYHA, heart failure etiology, ejection fraction, glomerular filtration rate, sex, ferritin, TSAT, CKD, diabetes mellitus, haemoglobin, BMI, enrolling country, race, atrial fibrillation, hospitalization for HF within past 12 months

5.5 Secondary Outcomes

All other secondary outcomes are listed and defined below. These secondary outcomes will be tested in the order listed below and are considered as supportive in the assessment of the effect size attributable to FCM and will be analysed in ITT only and without a multiplicity adjustment.

(1) Mean change in 6MWT distance from baseline to 12 months will be compared using linear regression adjusting for baseline value of 6MWT distance.

(2) Time to CV deaths or intervention for worsening heart failure (hospitalization or urgent heart failure visits) defined as time from randomization to the earliest of confirmed CV death or confirmed intervention for worsening heart failure will be compared using the Cox proportional hazards model.

(3) Time to CV deaths or CV hospitalizations defined as time from randomization to the earliest of confirmed CV death or confirmed CV hospitalization will be compared using the Cox proportional hazards model.

(4) Time to CV deaths defined as time from randomization to confirmed CV death (deaths confirmed as “Unknown” type will be included in the CV death counts) will be compared using the Cox proportional hazards model.

(5) Time to non-cardiovascular deaths defined as time from randomization to confirmed non-CV death will be compared using the Cox proportional hazards model.

(6) Time to first confirmed hospitalization for myocardial infarction (MI) defined as time from randomization to the earliest confirmed hospitalization for MI will be compared using the Cox proportional hazards model.

(7) Time to first confirmed hospitalization for stroke defined as time from randomization to the earliest confirmed hospitalization for stroke will be compared using the Cox proportional hazards model.

(8) Time to first confirmed hospitalization for other CV event defined as time from randomization to the earliest confirmed hospitalization for other CV event will be compared using the Cox proportional hazards model.

(9) Time to first confirmed urgent heart failure visit defined as time from randomization to the earliest confirmed urgent heart failure visit will be compared using the Cox proportional hazards model.

All time to event secondary outcomes will be analysed using the same approach as in the top secondary outcome analysis based on the ITT population. To assess change from baseline, a baseline measurement and the 12-month measurement both are required.

5.6 Hypophosphatemia Sub-study Analyses

A separate appendix to this SAP will detail analyses to be conducted in the Hypophosphatemia safety sub-study participants.

5.7 Exploratory Analyses

The below endpoints will be explored to further help interpret the primary analyses.

(1) Time to all cause death at one year defined as time from randomization to all cause death within 1 year (non-events censored at 1 year) will be compared using the Cox proportional hazards model.

(2) Number of heart failure hospitalizations at one year will be analysed using negative binomial regression analysis.

(3) Combination of all cause death and number of heart failure hospitalizations at one year will be analysed using the same method as used for the primary efficacy endpoint.

(4) Mean change in the 6MWT distance from baseline to six months will be compared using linear regression adjusting for baseline value of 6MWT distance.

(5) Time to all cause death through the duration of the study defined as time from randomization to all cause death (non-events censored at last known alive date) will be compared using the Cox proportional hazards model.

(6) Combination of CV death and total number of heart failure hospitalizations through the duration of the study will be analysed using the same method as used for the primary efficacy endpoint.

(7) Combination of CV death and total number of urgent heart failure events through the duration of the study will be analysed using the same method as used for the primary efficacy endpoint.

6 SAFETY ANALYSIS

There are no *a priori* hypotheses to be tested for safety. Safety will be assessed within the Safety population. Analyses visit-based Box and Whisker plots will be produced for continuous safety variables by randomized treatment where applicable. Shift tables for vital signs will be created for dosing days. Supplementary analyses will only be performed where these summaries suggest that there may be clinically significant differences.

For continuous safety parameters, at least one post-randomization measurement is required for inclusion in the analysis. To assess change from baseline, a baseline measurement is also required.

6.1 Adverse Events (AEs)

The original term used by investigators to identify non-serious AEs leading to discontinuation of study drug, or the SAEs, will be coded to the Preferred Term level using the Medical Dictionary for Regulatory Activities (MedDRA).

The treatment emergent serious adverse experiences (TESAE) are defined as those SAEs that have a start date on or after the date of first study medication administration. Events that have been determined as primary or secondary outcomes in the study are not regarded as SAEs for the safety analysis. Any adverse experience (AE) that does not meet the definition of SAE is considered non-serious. Non-serious AEs will not be collected for this trial except for AEs leading to cessation of study medication administration.

Summary of the following AEs will be provided by treatment group and by System Organ Class (SOC), Preferred Term (PT). These summaries will also be presented overall and by the subgroups of age, sex, race, and body mass index (BMI):

- All AEs (serious or non-serious resulting in discontinuation of study drug)
- All SAEs
- All TEAEs
- All TESAEs
- TEAEs (serious or non-serious) that result in discontinuation of study drug
- TESAEs considered related (possibly, probably or definitely) to study drug
- TESAEs with a fatal outcome.

We will also summarize severity, relatedness, seriousness criteria, and outcome at participant level for All TEAEs, the TEAEs categorized as below, all TESAEs, and All non-serious TEAEs.

TEAEs of Hypophosphatemia by SOC and PT
-MedDRA PT Blood phosphorus decrease
-MedDRA PT Blood phosphorus abnormal
-MedDRA PT Hypophosphatemia
-MedDRA PT Hypophosphatemic rickets
-MedDRA PT Rickets familial hypophosphatemic

TEAEs of Hypersensitivity/anaphylactoid reactions by SOC and PT
- MedDRA SMQ Anaphylactic reaction
- MedDRA SMQ Angioedema
- MedDRA PT of Hypersensitivity

TEAEs of Injection/infusion site reactions by SOC and PT
-MedDRA HLT Infusion site reactions
-MedDRA HLT Injection site reactions
-MedDRA HLT Administration site reactions NEC
-MedDRA PT Infusion related reaction

TEAEs of Medication error by SOC and PT
- MedDRA SMQ Medication errors

TEAEs of Hemosiderosis by SOC and PT
-MedDRA PT Hemosiderosis
-MedDRA PT Hematochromatosis
-MedDRA PT Iron overload
-MedDRA PT Hepatic siderosis
-MedDRA PT Cardiac siderosis
-MedDRA PT Pulmonary hemosiderosis
-MedDRA PT Superficial siderosis of central nervous system

6.2 Laboratory Data

- Descriptive statistics will be provided for central laboratory measurements as identified below at baseline and each scheduled (or reported) time point, and for changes from baseline by treatment. Grades based on most recent Common Terminology Criteria for Adverse Events (CTCAE) will be identified algorithmically for Haematology and Chemistry central laboratory data and will be summarized by visit using bar-chart and percentages. Shift tables will be provided for the max or min changes relative to baselines.
    a. Hematology: Hb, Hct, RBC, WBC, MCV, MCH, MCHC, RDW, platelets, differential count, and reticulocyte count
    b. Chemistry: Sodium, potassium, chloride, BUN, creatinine, albumin, alkaline phosphatase, total bilirubin, GGT, AST, ALT, LDH, calcium, phosphorus, glucose, bicarbonate, and magnesium
    c. Iron indices: Serum iron, serum ferritin, total iron binding capacity (TIBC), and percentage serum transferrin saturation (TSAT)
    d. Other: 1,25 (OH)2 Vitamin D, 25 (OH) Vitamin D, Parathyroid Hormone, NT-proBNP

6.3 Previous and Concomitant Medications and Interventions

Concomitant medications and interventions to be summarized for ITT and Safety. Baseline and post-baseline determination will be made programatically in reference to randomization date and assessment date(s).

- Concomitant medications of interest at baseline will be summarized by treatment.
- Post baseline concomitant medications of interest will be summarized by treatment and nominal visit.
- Post baseline concomitant intervention will be summarized by treatment and nominal visit.

6.4 Vitals and Physical Assessments

- Descriptive statistics will be provided for vital sign and targeted physical exam measures: systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, body weight, and BMI at baseline and at each scheduled time point and for change from baseline by treatment.
- Shift tables for SBP and DBP will be provided for the dosing days

6.5 Drug Exposure

The following types of treatment durations will be calculated for FCM and placebo arm.

- Total treatment duration (including days off study drug) = Number of days between the first and last injection (last injection date – first injection date) +1
- Treatment duration (excluding days off study drug) = Number of days of taking study drug as calculated above, minus the total duration of study drug interruption (each duration of dose interruption is calculated as: (injection restart date – temporary injection stop date) +1.
  Temporary injection stop date is the first visit date at which an injection is not given.
  An injection restart date is when the injection is given following a temporary stop date.
- Total observation duration = Number of days in the study (date of final study disposition –date of randomization) +1.

We will also summarize the total number of infusions received and cumulative dose by treatment for the participants.

Kaplan Meier estimates of time to permanent study drug discontinuation will be summarized by treatment.

Frequency rates of participants, whose treatment was switched due to improved iron indices or whose drug dosage was decreased through the study will be provided by treatment.

Summaries of duration of treatment, study drug interruption, and drug compliance will be provided by treatment through the overall study period in Safety Population.

6.6 Events of Special Interest related to HF that did not lead to Hospitalization

- All events of interest related to HF that did not lead to hospitalization collected in the study will be summarized by treatment. Specifically, the events are: supraventricular arrhythmia, ventricular arrhythmia, and renal failure, all requiring urgent/emergent intervention.

6.7 Hospitalizations not part of Primary and Secondary Outcomes

- All hospitalizations collected in the study that do not comprise primary or secondary outcomes (non-CV hospitalizations) will be summarized by treatment.

6.8 COVID-19 Related

Any deviations from the protocol related to COVID-19 will be summarized by treatment and a listing will be generated. Listings of all participants recorded as impacted by COVID-19 (related to visit completion, early study or treatment discontinuation, inability to complete 6MWT, and any reported adverse events of COVID-19) will also be provided, as appropriate.

6.9 Other Safety Assessments

All adverse events of special interest (ventricular tachycardia, supraventricular tachycardia, and renal failure, all requiring urgent/emergent intervention) will be summarized at participant level by treatment.
If participant or participant's partner becomes pregnant while on the study, the information will be included in the narratives and no separate table will be provided.

7 DATA SAFETY MONITORING BOARD AND INTERIM ANALYSES

7.1 Interim Analyses

A Data and Safety Monitoring Board (DSMB) Committee will review safety data, including a tally of the composite outcome events at least every 6 months. The DSMB can recommend stopping the study for safety concern at any point. In addition, one interim analysis is planned to determine if an early stopping for an overwhelming efficacy should be recommended or if an increase in sample size is warranted. The details as identified in Section 8.10 of the protocol are that this analysis will be conducted after 2250 (75%) participants have been randomized. Significance level will be set at 0.0001 for this analysis, resulting in an adjusted significance level for the final analysis of 0.0099 for the primary endpoint and 0.0499 for the first secondary endpoint, preserving the overall significance at 0.01 and 0.05, respectively. Conditional power will be estimated based on data accrued to date and presented to the DSMB.
The DSMB may recommend that the study continues as planned, discontinue the study, or that the trial be continued with recommended changes to the protocol.
The Executive Steering Committee will determine if an increase in sample size is warranted in order that at least 771 participants will experience an event of CV death or hospitalization for heart failure.

8 DATABASE SOURCES

The HEART-FID clinical database will be housed in RAVE Electronic Data Capture (EDC) hosted by Duke Clinical Research Institute (DCRI). In addition, DCRI and KCR will obtain protocol deviation from CTMS, the central laboratory data from Covance, and the CEC data from the DCRI CEC group. DCRI will obtain unblinded randomization data collected in the Interactive Web Response System (IXRS) from Almac after the database is locked at the end of the trial.

9 REFERENCES

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10 APPENDICES

Additional Appendices will be produced separately and finalised following finalisation of SAP but before database lock.

10.1 Appendix 1: Summary of Amendments to the Protocol relevant to the SAP are here. Details can be found within the CSP.

Protocol Version 2 and 3:

Affected Sections	Summary of Revisions
Appendix 1	Added a sub-study protocol to evaluate hypophosphatemia.
8.10 Stopping Rules and Interim Analysis	The DSMB may recommend that the study continues as planned, discontinue the study or that the trial be continued with recommended changes to the protocol. The Executive Steering Committee will determine if an increase in sample size is warranted in order that at least 771 participants will experience an event of cardiovascular death or hospitalization for heart failure.
4.5 Discontinuation from Study Drug	Added a definition for a participant permanently discontinued from the study.

10.2 **Appendix 2:** Simulations for power estimation for the primary endpoint were conducted at the time of writing the original version of the CSP. The below detailed information was used at the time.

Clinical Rationale: The proposed composite endpoint is intended to capture the clinical effects of the proposed treatment of participants in heart failure with reduced ejection fraction with iron deficiency with or without anemia. From a participant's and clinician's perspective, the essential elements are aimed towards improving the health and well-being of participants with disease as complex as heart failure with reduced ejection fraction. By targeting the experience of participants with heart failure as measured by survival, burden of heart failure hospitalizations, and functional status the proposed composite end-point reflects the key characteristics of a robust composite endpoint (Anker 2016). The rationale for including the burden of hospitalizations is based on the well-recognized problem that recurrent hospitalizations for worsening heart failure are a common occurrence in participants, and they impose a substantial clinical burden on participants and their families as indicative of worsening of their condition (Gheorghiade 2013). Despite the importance of repeat events, they are often ignored in the majority of clinical trials in favour of 'time to first event' analyses (Zannad 2013). In addition, heart failure is characterized as a disorder with significant functional impairment in physical activities. One of the most robust assessments of functional impairment that may be feasible on a large scale is the 6MWT (Forman 2012). This standardized assessment has been used to define functional status and stratify risk for participants in heart failure as well as other conditions such as pulmonary hypertension. The use of this hierarchical, composite endpoint will enable us to provide a more robust and clinically-meaningful classification of participants with heart failure with iron deficiency into those who have improved, remained unchanged, or have deteriorated based on survival, burden of hospitalizations with heart failure, and functional status as measured by the 6MWT distance.

Methods:
Each participant from the treatment arm gets compared with each participant from the control arm based on the 12-month experience to determine treatment response per the following hierarchy:

1. CV death

   If both die, the one who survives longer is better off;
   If one dies, the one that survives is better off;
   If neither dies, examine hospitalizations.

2. Hospitalization for worsening heart failure

   The one with fewer hospitalizations is better off;
   If number hospitalized equal (both not hospitalized, both with 1 hospitalization etc.), compare 6MWT;

3. Change in 6MWT

   The one with higher change in 6MWT is better off;

Statistical Test
The main comparison will be conducted using the Wilcoxon-Mann-Whitney test. The comparison of individuals in the treatment versus control arms is equivalent to ranking all individuals according to their experience. At one end of the ranking are individuals with the best experience - those alive and not hospitalized for worsening heart failure ordered according to their improvement in 6MWT; at the opposite end are those who die ordered according to their survival time. Those alive but hospitalized are in the middle, ordered according to their number

of hospitalizations for worsening heart failure and then by their change in 6MWT. The non-parametric Wilcoxon-Mann-Whitney test sums the ranks of those in the treatment arm and compares them with the sum of ranks in the control arm.

Table 10.2.1 Assumptions for Sample Size Calculations

Ranked tier at 12-month endpoint	Control	Treatment
Death total	8%	6.8%
Death without hospitalization	4%	3.4%
Death with hospitalization	4%	3.4%
Hospitalizations in survivors		
1	6%	4.8%
2	3%	2.4%
3 or more	1%	0.8%
Change in 6MWT	Mean = 0 SD = 90	Mean = 18 SD = 90
Empirical Power: 0.9500 (N=2930, α=0.0025) Clinically-Meaningful Difference: 0.068/0.08 = 0.85		

Conclusion
With 3000 participants (1500 per arm) and 2.5% annual loss to follow up, our simulations estimate ≥90% power at various two-sided significance levels between 0.0025 and 0.01.

10.3 Appendix 3: Ranking Algorithm (primary efficacy endpoint)

Scenario	Participant: i/j	All-cause Mortality (1 year)	Survival Times (from baseline)	Cardiovascular-related hospitalization (1 year)	6 month change in 6MWT	Score
1	i	Dead	Low	not in consideration	not in consideration	-1
	j	Dead	High	not in consideration	not in consideration	+1
2	i	Dead	not in consideration	not in consideration	not in consideration	-1
	j	Alive	not in consideration	not in consideration	not in consideration	+1
3	i	Alive	not in consideration	High	not in consideration	-1
	j	Alive	not in consideration	Low	not in consideration	+1
4	i	Alive	not in consideration	Tied	Low	-1
	j	Alive	not in consideration	Tied	High	+1

Statistical Analysis Plan

for

Heart Failure with Iron Deficiency (HEART-FID).

Version: 1.3

Date: 6 March 2023

Clinical Study Protocol/Amendment No: 1VIT15043/3

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF INJECTAFER® (FERRIC CARBOXYMALTOSE) AS TREATMENT FOR HEART FAILURE WITH IRON DEFICIENCY.

Prepared by: CT Statistics Group
[Duke Clinical Research Institute]

Prepared For: American Regent, Inc.
[Sponsor]

Statistical Analyses Plan Amendment x

The original Statistical Analysis Plan was finalized and issued on 21/Sep/2021. Major changes and clarifications of planned analyses in SAP V1.2 since the original SAP are listed below. All changes to the SAP have been instituted prior to unblinding of the HEART-FID study

Version	Date	Author(s)	Brief Summary of Changes
V1.0	21/Sep2021	[redacted]	Final version after American Regent's final comments on 14/Sep/2021. Signed.
V1.1	03/Oct2022	[redacted]	• Added baseline covariates to be used for model adjustment in section 4.1 • Updated references across the SAP to analysis visits to nominal/scheduled visit • Added sub-group categories • Added sensitivity tipping point analysis for key secondary • Added win-ratio analyses for hierarchical primary endpoint • Added clarity for tipping point analyses for hierarchical primary endpoint • Removed the inaccurately placed Finkelstein reference
V1.2	31/Jan2023		• Section 1.4: edit on alpha usage based on FDA feedback • Section 4.1: added clarifications about handling of missing data on covariates. Secondly added empirical curves to address FDA feedback. • Section 4.3: edit for clarity • Section 4.4.1: Couple of updates to add clarity about baseline 6MWT and address FDA feedback. • Section 4.4.2: removed the last line based on edits in section 4.1 and 4.4.1 • Section 5.3.1: Added a new sensitivity analyses in 5.3.1.5 to address FDA feedback. Downstream section numbering updated based on this. • Section 5.3.2: updated alpha for top secondary to 0.04 based on FDA feedback. • Section 5.4: updated the cut-off points to 2 of the sub-groups based on FDA feedback. • Section 5.7: clarification regarding ITT population added. Exploratory endpoints 8-13 added based on FDA feedback on the SAP V1.1. • Section 6.2: Minor clarifications added
V1.3	6/Mar2023		• Updated the language towards the end of section 1.4 which describes the alpha

			to be used for primary and top secondary analyses • Clarified that the alpha mentioned in section 7.1 is from the protocol and will not be used for the final analyses.

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LIST OF ABBREVIATIONS

6MWT	6 Minute Walk Test
ADaM	Analysis Data Model
AE	Adverse Experience
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CEC	Clinical Events Committee
CKD	Chronic Kidney Disease
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DCRI	Duke Clinical Research Institute
DSMB	Data and Safety Monitoring Board
EDC	Electronic Data Capture
FCM	Ferric Carboxymaltose
GGT	Gamma-Glutamyl Transferase
Hb	Haemoglobin
Hct	Haematocrit
HF	Heart Failure
HLT	High Level Term
HR	Hazard Ratio
HS	Hypophosphatemia Sub-study
ICH	International Council for Harmonisation
ITT	Intent-To-Treat
IV	Intravenous
IXRS	Interactive Web Response Systems
LDH	Lactate Dehydrogenase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NYHA	New York Heart Association
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cell
RDW	Red Cell Distribution Width

SDTM	Study Data Tabulation Model
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SD	Standard Deviation
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
TESAE	Treatment Emergent Serious Adverse Experiences
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
WBC	White Blood Cell

1 INTRODUCTION

HEART-FID is a double-blind, multicenter, prospective, randomized, placebo-controlled study to assess the effects of intravenous (IV) ferric carboxymaltose (FCM) compared to placebo on the hierarchical, composite endpoint of 12-month rate of death and hospitalization for worsening heart failure (HF) and change in 6 minute walk test (6MWT) at 6 months for participants in HF with reduced ejection fraction and with iron deficiency. The reader of this Statistical Analysis Plan (SAP) is also encouraged to read the corresponding protocol (1VIT15043, version 3.0, 11 January 2021) which provides detail on the conduct of the study, the operational aspects of clinical assessments, and the timings of individual participant assessments.

This SAP contains definitions of analysis populations, and details on the statistical methods for the analyses and summaries of study data that are to be performed, to help support the completion of the final Clinical Study Report (CSR) for study 1VIT15043. Details regarding analysis of the hypophosphatemia sub-study can be found in a supplemental SAP. Information on important definitions and reporting conventions and table shells to support the SAP will be in a supplemental Appendix.

Specifications of supporting tables, figures, and data listings are contained in a separate document.

Outcomes that are confirmed by clinical events classification (CEC) adjudication, the process for which is governed by specific charters referenced in the protocol, will be referred to as "confirmed" events in the SAP. The term outcome is used throughout this document as synonymous with the term endpoint used in the clinical trial protocol. The following events are confirmed by the CEC in HEART-FID: Death (Cardiovascular [CV] and Non-Cardiovascular), Cardiovascular Hospitalizations (Heart Failure, Acute Myocardial Infarction [MI], Stroke, and Other cardiovascular hospitalizations), and Urgent Heart Failure Visit. CEC data take precedence over investigator data when both are available and investigator response is different from the CEC adjudicated response.

1.1 Study Objectives

1.1.1 Primary Objective

To determine the efficacy and safety of iron therapy using intravenous (IV) FCM, relative to placebo, in the treatment of participants in heart failure with reduced ejection fraction and with iron deficiency.

1.1.2 Secondary Objective

To evaluate the effect of IV FCM, relative to placebo, on the functional capacity of participants in heart failure with reduced ejection fraction and with iron deficiency.

1.2 Study Design

This is a double-blind, multicenter, prospective, randomized, placebo-controlled study to assess the effects of IV FCM compared to placebo on the 12-month rate of death, hospitalization for worsening heart failure, and change in 6MWT from baseline at 6 months for participants with heart failure, reduced ejection fraction, and with iron deficiency.

After an initial screening period of up to 28 days, eligible participants will be stratified by region and randomized in a 1:1 ratio to FCM or placebo. Study drug administration will occur on Day 0 and Day 7 as an undiluted slow IV push, with additional study visits (in person or via telephone) planned at 3 month intervals, and additional dosing administered every 6 months as applicable (based on dose regimen below).
For all participants, laboratory tests for haematology, ferritin, and transferrin saturation (TSAT) with appropriate safety evaluations, to determine additional treatment, will occur at 6 month intervals.

In a subset of sites, a sub-study will be conducted to characterize serum phosphate levels over time in participants in heart failure with reduced ejection fraction with iron deficiency after dosing with FCM. There will be additional visits for these participants during the first 6 months (Clinical Study Protocol [CSP] Appendix 1, Section 3.3)

Initial treatment will occur on Day 0 and Day 7. On Day 0 and 7, Group A (FCM) will receive a 750 mg undiluted, blinded dose of IV FCM at the rate of approximately 100 mg (2 mL)/minute (approximately 7 minutes 30 seconds); Group B (placebo) will receive a blinded placebo (15 cc of normal saline) IV push at 2 mL/minute (approximately 7 minutes 30 seconds). Participants in Group A with body weight <50 kg (110 pounds) will have individual FCM doses adjusted to 15 mg/kg, not to exceed an individual dose of 750 mgs or a cumulative dose of 1500 mg per treatment cycle. Placebo dosing will be adjusted for weight based on volume.

All participants randomized will be dosed every 6 months. Participants randomized to the FCM arm will be dosed as indicated based on haemoglobin levels (i.e. Hb <13.5 g/dl [females] or <15.0 g/dl [males)]) and iron studies (i.e. serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20%). Participants not meeting pre-specified laboratory criteria for blood counts and iron studies and all participants randomized to the placebo arm will be administered IV placebo infusion at each visit.

Unblinded site personnel, responsible for preparation and administration of the FCM or Placebo, will ensure that the participant and all blinded site staff are not able to observe the preparation or administration of study treatment.

1.3 Randomization and Blinding

The randomization scheme was generated by a statistician at DCRI who is firewalled to the operational team, using Statistical Analysis System (SAS v9.4) with region as the only stratification field. Blocking was used in the scheme with random block sizes (3 different levels). This scheme was implemented into the Interactive Web Response Systems (IXRS) by the vendor Almac. The vendor maintains randomized treatment assignments as well as unblinded kit dispensation information. The operational team for this trial is to remain blinded until data base lock, at which time the unblinded treatment codes received from Almac will be combined with blinded data.
In the event of the need to break an individual participant blind, the site can call Almac for this information. The operational team gets informed if such unblinding occurs; however, they do not know the true treatment assignment.
The 3 regions are defined within the randomization scheme as follows (Details can be found in the SAP Appendix for Definitions and Reporting Conventions):

- North America
- Asia Pacific
- Europe

1.4 Sample Size and Power

The study design allows for sufficient power for both the primary and top secondary outcomes. Numerical simulations based on multivariate normal vectors (Appendix 2) were conducted to estimate power for the primary treatment comparison based on the following assumptions about events rates described in **Table 1.4.1**

Table 1.4.1. Assumptions about Event Rates for Primary Outcome

Ranked tier at 12-month endpoint (6 month for 6 MWT)	Control	Treatment
Death total **Death without hospitalization** **Death with hospitalization**	8% 4% 4%	6.8% 3.4% 3.4%
Hospitalizations in survivors **1** **2** **3 or more**	 6% 3% 1%	 4.8% 2.4% 0.8%
Change in 6 Minute Walk Test	Mean = 0 SD = 90	Mean = 18 SD = 90

With 3014 participants (1507 per arm) and 2.5% annual loss to follow-up for clinical outcomes and 15% of individuals with missing 6MWT at 6 months (unable to perform or lost to follow-up), projected simulations estimate 90% power at an overall two-sided significance level of 0.01, accounting for one interim analysis as described in Section 7.1.

For the top secondary composite, there is an assumed event rate of 0.0128 per month in the control arm which represents conservative 75% discounting of the event rate obtained by the FCM meta-analysis [Anker 2015]. The anticipated hazard ratio (HR) was set at 0.80 (20% reduction). Uniform enrollment was assumed over the period of 30 months, with an anticipated minimum follow-up of 12 months (required minimum of 6 months), anticipated maximum follow-up of 42 months (no required maximum), and monthly loss to follow-up of 0.0021 (2.5% annualized). With these assumptions, 1500 per study arm (3000 total) provides 90% power to reject the null hypothesis of no difference between treatment arms when tested at an overall two-sided level of significance α=0.05, accounting for one interim analysis as described in Section 8.10 of the CSP. This results in a total of 771 participants with events (in case of multiple events experienced by a participant, only their first one will be counted towards the 771) necessary to achieve the desired power. Thus, the trial has the potential opportunity to be stopped at a point where the projected number of participants reaches 771 events, but no earlier than the last participant reaching 12 months of follow-up.

In order to maintain an overall alpha of 0.01 and account for interim analysis we will use a two-sided alpha of 0.0099 for the final analysis of the primary endpoint.

At the request of the FDA, the overall alpha for the top secondary endpoint was changed from 0.05 to 0.04. In order to maintain an overall alpha of 0.04 and account for interim analysis we will use a two-sided alpha of 0.0399 for the final analysis of the top secondary endpoint.

1.5 Schedule of Major Assessments

Following randomization, outcomes and serious adverse event data are collected at 90 days and at every 6 monthly visit as detailed in schedule of events (Section 3.3 of the CSP)

1.6 Summary of Relevant Amendments to the Protocol

Please refer to Appendix 1 for this information. The version the participant was enrolled under will be available in the database.

2 ANALYSIS SETS

2.1 Intent-to-treat (ITT) Population

The ITT population consists of all participants randomized to a treatment group in the study regardless of their compliance with the study medication. The participants are analysed in the treatment group to which they were randomized. This is the primary population of all efficacy analyses.
Any participant who gets a treatment assigned via the IXRS will be considered to have been randomized.

2.2 Safety Population

The Safety population will consist of all ITT participants who received at least 1 dose of study medication identified by the presence of injection start date. When summarizing data using this population, participants are analyzed in the As Treated group. If a participant receives any FCM study drug, then the participant will be counted as treated in the FCM arm, regardless of the amount of medication received; otherwise the participant will be counted as treated in the placebo arm.
The Safety population will be used for assessing Safety.

2.3 Per-protocol (PP) Population

The Per-Protocol Population is a subset of the ITT population excluding participants who complied with the randomized treatment for less than 50% of the dosing prior to 1 year follow-up. In cases of medication error, treatment assignments in the per-protocol analysis will be analyzed according to the actual treatment received as the first study drug dose.

2.4 Hypophosphatemia Sub-study (HS) Population

The Hypophosphatemia Sub-study (HS) population will consist of all ITT participants who enrolled in the sub-study identified by the presence of injection start date. When summarizing data using this population, participants will be analyzed according to the actual treatment received as the first dose.
The HS population will be used for assessing Safety.
Please see the HS SAP for further details.

3 BACKGROUND CHARACTERISTICS

3.1 Disposition of Participants

Disposition data will be summarized for all randomized participants. The summary by treatment will include

- Inclusion in the four study populations
- Participants completing study alive
- Lost to follow up
- Withdrawn consent for follow up
- Reason study drug permanently discontinued

3.2 Demographic and Baseline Characteristics

The demographic, baseline clinical and anthropometric characteristics collected in the study will be tabulated and summarised as descriptive statistics by treatment for both ITT and Safety populations.

3.3 Medical History

Participant medical history will be summarized within both ITT and Safety populations.

- Duration of HF calculated as (year of randomization – year of onset) +1 and etiology of HF at baseline will be summarized by treatment.

All other medical history data collected in the study will be summarized by treatment group.

4 METHODS OF ANALYSIS

4.1 General Principles

In addition to specific analyses and presentations that are detailed in the following sections, results will be summarised using descriptive statistics, including the number of participants, mean, standard deviation, median, and range as appropriate. For categorical variables, counts and percentage per treatment group will be presented.

Summaries of continuous characteristics will be based on non-missing observations. Percentage for categorical variables will be calculated based on number of participants with non-missing values for the variable.

Unless otherwise stated, timings of efficacy endpoints will be relative to the date of randomization. Specifically, for all time-to event analyses (defined as [event date – randomization date] +1 where event occurs and as [appropriate censoring date based on analytic population – randomization date] +1 where event does not occur), the treatment groups will be analysed using a Cox proportional hazards model that includes treatment as an explanatory factor, region as stratification factors along with pre-specified baseline covariates: age, sex, ejection fraction, NYHA class, heart failure etiology (Ischemic vs. non-ischemic (unknown etiology considered as non-ischemic)), NT-proBNP, haemoglobin, ferritin, TSAT, eGFR and BMI, unless specified otherwise. If any of the pre-specified baseline covariates have >5 participants with missing data, they will not be used in the analyses to maintain the ITT population for the model. If the baseline covariate is missing data on <= 5 participants, we will impute the missing value with overall mode if categorical covariate and the overall mean if continuous variable. The Efron method will be used for handling ties. P-value and confidence intervals for the HR will be based on the Wald statistic. Any analyses using events that are confirmed by the CEC will use the CEC adjudicated responses and related dates. Analyses of Cardiovascular (CV) death, will include deaths with cause of death confirmed as unknown.
In addition, the summary tables of these analyses will include the number of participants with event and the cumulative incidence (1 – the "survival" or event-free proportion) over time per treatment group presented annually through the last time point where 90% of the overall events have occurred. Cumulative incidence function and Kaplan-Meier estimates of participants with events will also be calculated and plotted through maximum follow up available in the study, with number of participants at risk indicated below the plot at specific times.
We will present empirical cumulative distribution function curves by treatment of change in 6MWT distance at 6 and 12 months.
For all the hierarchical composite endpoints, in addition to primary analytic method, we will present win-ratio along with its confidence interval.
The timing of safety data will be relative to the study drug start date. Specifically, any time to safety event durations will be defined as [event date – study drug start date] +1 where event occurs and as [appropriate censoring date based on analytic population – study drug start date] +1 where event does not occur).
Baseline is defined as response/value collected closest to randomization and on or prior to study drug start. If both date and time are available we will use the value prior to the first study drug start date time. However, if only dates are available, we will use the values on or prior to first study drug start date as the baseline. Any measures (for example central labs) without a value in this window will have a missing baseline value.
End of study date for the participant will be driven off of the date of their final study disposition. Date of last contact for the participant will be driven off of their last visit

performed, these dates can be different from the date last known alive collected on end of study form for withdrawn consent participants.
The median and total person-years of follow-up for the whole study will also be reported.

All analyses included in this SAP will be performed using SAS v9.4 or higher. They will be based on Clinical Data Interchange Standards Consortium (CDISC) standard data (Analysis Data Model (ADaM) and/or Study Data Tabulation Model (SDTM)). The summaries will be presented as either tables or, where appropriate, as figures. International Council for Harmonisation (ICH) required listings will also be produced.

- "n" will be displayed as a whole number
- The Mean, SD, Median, Q1, and Q3 will be displayed with 1 more decimal place than the source data precision.
- The Min and Max will be displayed with the same number of decimal places as the source data. Any other presentation of raw data will be also be displayed with the same decimal places as the source data.
- All tests and confidence intervals are 2-sided unless specified otherwise.
- All p-values will be displayed with three decimal places.
- All by visit summaries and analyses will use scheduled/nominal.

4.2 Multiple comparisons

We will complete multiplicity adjustment as noted in the CSP Section 8.8. The primary and top secondary outcomes will be tested sequentially, and thus, no multiplicity adjustment is necessary

4.3 Right Censoring

In this study we expect missing outcome data to be infrequent and every effort will be made to collect all information regarding the primary outcomes prior to study termination, even in those who have discontinued the study treatment.

For all analyses covered by this SAP, the observation time for participants who have not had an event in the analysis of a specific outcome will be right censored at the date of last contact where any elements of the outcome could be assessed unless otherwise specified. Same algorithm will be followed for inclusion of events in the analyses.

Note that for the analysis of the components of the primary composite outcome, participant exposure will be censored at the date of the occurrence of the component outcome of interest.

Note that for outcomes not including CV death, all deaths are censoring events.

In safety time-to-event analyses in the Safety population, participants who have not had the event in question will be censored following same rules as detailed for the ITT population.

4.4 Handling of Missing Data

4.4.1 Outcome Data/Dates

The primary analysis will rely on a multiple imputation model, with Markov chain Monte Carlo algorithm based on the totality of observed data. One exception to this rule will be that

individuals unable to perform the 6MWT test at 6 months i.e. those who did not perform a 6MWT or died prior to 180 days will have their value imputed as the worst possible 6MWT distance which is 0 meters. Any missing death dates will be imputed using date imputation rules in this section. A baseline 6MWT distance is needed to be able to calculate change from baseline 6MWT, hence, any missing baseline 6MWT distance will be imputed as overall mean to allow full ITT population to be included in primary analyses.

The SAS PROC MI procedure will be used for multiple imputations on the 6 month 6MWT distance, with 20 imputations. To ensure consistency in the imputed data for future possible validations, a seed number will be fixed to 1000. Baseline 6MWT, treatment and region will be included as covariates in the imputation model. We will include all observed data in the imputation model with the exception of participants unable to perform 6MWT at 6 months who will have their 6MWT distance included as 0 meters before performing multiple imputation. Imputed data set(s) will include an index variable to identify the number of imputed data. The results across the imputed datasets will be combined using Rubin's rule (Rubin 1987) to obtain one set of results for the primary analysis. These same missing data handling rules will be used for the Win-Ratio analyses. Basic statistics on the overall original data (incomplete data) and the data following imputation will be provided in the Clinical Study Report (CSR).

For secondary efficacy endpoints, missing data relating to the indicator for the confirmed composite CV outcome and/or its components will not be imputed. Any partial or completely missing date for a confirmed composite CV outcome at the time of database lock will be imputed as follows:

- If the day is missing, 15th of the month, or the randomization date (if participant randomized after 15th of the same month and same year) will be used, making sure the imputed date is not post date last known alive on end of study form;
- If the month is missing, June, or the randomization month (if participant randomized after June and year of the event is same as randomization year) will be used, making sure the imputed date is not post date last known alive on end of study form;
- If the complete date is missing, the midpoint between randomization and the date of last known event-free visit will be used with the exception of death date.
- If the death date is completely missing, it will be imputed to be the date after last contact date.

4.4.2 Other Missing Data

Any other partial date of relevance (for example, date of last study contact at the time of database lock will be imputed as follows:

- If the day is missing, 15th of the month, or the randomization date (if participant randomized after 15th of the same month and same year) will be used, making sure the imputed date is not post end of study date.
- If the month is missing, June, or the randomization month (if participant randomized after June and year of the event is same as randomization year) will be used, making sure the imputed date is not post date last known alive on end of study form.

4.5 Assessment of Model Assumption

The validity of the proportional hazards assumption made in the secondary analysis will be examined using standard graphical methods such as Log (-log) plots; if the assumption holds the curves should be approximately parallel to each other.

An additional analytical method that includes treatment*log (time) as a factor in the model and tests the interaction factor at the 0.05 significance level may be employed; non-significance ($p>0.05$) of this factor would suggest proportionality.

If there is evidence of non-proportionality its cause will be investigated by exploring hazard ratios within few pre-specified clinically meaningful time landmarks such as every six months.

5 OUTCOMES

Please refer to Section 10.2 of the CSP for information on which endpoints are adjudicated.

5.1 Primary Outcome

The primary outcome follows an ordinal scale of clinical severity comprised of 1) confirmed death at one year, 2) number of confirmed hospitalizations for heart failure evaluated at one year; or 3) change in 6MWT from baseline evaluated at 6 months.

We will rank all participants from the lowest to the highest based on their 12-month experience, regardless of their treatment assignment.

Each participant from the treatment arm gets ranked/compared with each participant from the control arm based on the 12-month experience for Death and Hospitalizations for heart failure and 6 month results for change in 6MWT to determine treatment response per the following hierarchy:

1. Death

If both die, the one who survives longer is better off;
If one dies and one does not, the one that survives is better off;
If neither dies, examine hospitalizations for heart failure.

2. Hospitalizations for heart failure

The one with fewer hospitalizations is better off
If neither has been hospitalized for heart failure or the number heart failure hospitalizations is equal, compare change in 6MWT.

3. Change in 6MWT

The one with higher change in 6MWT is better off;

Any ties that cannot be resolved by change in 6MWT remain as ties.

5.2 Top Secondary Outcome

The top secondary outcome is defined as the time from randomization to the onset of first confirmed event in the composite CV outcome of CV-related death (any deaths confirmed as unknown are included in CV deaths) or hospitalization for heart failure.

In the unlikely event that two confirmed outcomes occur on the same day, the following hierarchy will be used to ascribe the primary component of the composite:

- CV-related death
- Hospitalization for heart failure

5.3 Analyses of the Primary and the Top Secondary Outcome

The analytic approaches for the primary and top secondary outcome are detailed in below sections.

5.3.1 Nonparametric Test of FCM vs. Placebo for Primary Composite

The null hypothesis being tested is that a randomly chosen participant in the treatment arm is equally likely to be ranked better or worse than a randomly chosen participant in the control group. The two-sided alternative is that the participant is not equally likely to be ranked better or worse.

In addition to performing the test, we will estimate the probability that a participant in the treatment arm has a better rank than a participant in the control arm and its corresponding confidence interval.

The main comparison will be conducted using the Wilcoxon-Mann-Whitney test in ITT population relying on multiple imputation model as summarized in Section 4.4.1.

The above comparison of participants in the treatment versus control arms is equivalent to ranking all participants according to their experience. At one end of the ranking are participants with the best experience - those alive and not hospitalized for worsening heart failure ordered according to their improvement in 6MWT; at the opposite end are those who die ordered according to their survival time. Those participants alive but hospitalized are in the middle, ordered according to their number of hospitalizations for worsening heart failure and then by their change in 6MWT. The non-parametric Wilcoxon-Mann-Whitney test sums the ranks of those in the treatment arm and compares them with the sum of ranks in the control arm.

Win-Ratio and its confidence intervals will be calculated to aid in interpretation of the results for primary efficacy analysis. The unmatched pair win ratio will be calculated by adding all wins from treatment group and dividing it by all wins from placebo group. The confidence interval will be calculated using the supplementary material for the reference (Pocock 2012).

In all analyses, the number of hospitalizations (and the number of days in the hospital in the sensitivity analysis described in Section 5.3.1.1) will be adjusted for the time in follow-up. This will be accomplished by dividing the observed number by time at risk in years. For individuals who complete the pre-specified 12 months of follow-up, time at risk equals 1. For all others, it is equal to the fraction of 12 months that the person remained in the study.

5.3.1.1 Sensitivity Analysis (Additional Layer to Hierarchy) for Nonparametric Test of FCM vs. Placebo for Primary Composite

In a sensitivity analysis we will add another layer to the hierarchy described above – in individuals who have been hospitalized for heart failure during follow-up, ties in the numbers of hospitalizations will be resolved based on the total number of days in the hospital during follow-up, before proceeding to comparison of differences in the 6MWT using the primary analytic method. This will be conducted in the ITT population only.

5.3.1.2 Sensitivity Analysis for Potential Covid-19 Impact for Nonparametric Test of FCM vs. Placebo for Primary Composite

In case there are 5% or more of randomized participants with missing 6 month 6MWT due to COVID-19 (those with visits not performed or visit type modified due to Covid-19) who also did not have a qualifying clinical event (death or heart failure hospitalization through 1 year), then we will assess the sensitivity of primary results to the missing 6MWT data by conducting a tipping point analyses on the primary analyses method in ITT population.
The tipping point analysis will assume progressively biased tie breaking for 6MWT distance missing due to COVID-19 varying from worst distance favouring the placebo to the best distance. Hence, starting with all missing 6MWT values favouring the placebo to break the tie and checking if this does not change inference from the primary analyses. However, if it does change the inference then we will continue going down the scale to find the tipping point. The 6MWT distance at 6 months missing for non-COVID-19 reasons will be imputed as for primary analysis.

5.3.1.3 Sensitivity Analysis for Russia Ukraine War Impact (censor the data after invasion) for Nonparametric Test of FCM vs. Placebo for Primary Composite

We plan to conduct two different sensitivity analyses to assess the impact of the Russia-Ukraine war. In the first of these two analyses we will censor the data from Russia and Ukraine for the hierarchical primary composite endpoint with a date after invasion (24 February, 2022), before proceeding to comparison of the endpoint using the primary analytic method. This will be conducted in the ITT population only.

5.3.1.4 Sensitivity Analysis for Russia Ukraine War Impact (exclude participants from these two countries) for Nonparametric Test of FCM vs. Placebo for Primary Composite

As a second sensitivity method to assess the impact of the war on the hierarchical primary composite, we will exclude participants from Russia and Ukraine for comparison of the endpoint using the primary analytic method. This will be conducted in the ITT population only.

5.3.1.5 Sensitivity Analysis to account for Clinically Meaningful Difference in Change from Baseline in 6MWT for Nonparametric Test of FCM vs. Placebo for Primary Composite

In this sensitivity analysis of hierarchical primary composite, we will use the win-ratio method with the additional condition of requiring a change from baseline in 6MWT for the participant to be 10 and 20 meters respectively to be considered clinically meaningful (Khan 2022). Hence, if two participants are tied based on their data on death time and number of HF hospitalizations within 1 year, further tie-breaking will require 10 meters and 20 meters difference in 6MWD change when they are compared for win-ratio analysis. Only the win-ratio and its 95% confidence interval will be computed. This analysis will be conducted in the ITT population only.

5.3.1.6 Key Supportive Analysis for Nonparametric Test of FCM vs. Placebo for Primary Composite

As the key supportive analysis, the null hypothesis for the primary composite end point, that a randomly chosen participant in the treatment arm is equally likely to be ranked better or worse than a randomly chosen participant in the control group, will be tested using the same approach as in the primary analysis based on PP population.

In case of a difference in inference between the primary analysis and the key supportive analyses, further exploratory analyses will be conducted to understand the reason for a possible difference.

5.3.1.7 Supportive Analysis (Impute to Worst Possible 6MWT Distance at 6 Months) for Nonparametric Test of FCM vs. Placebo for Primary Composite

As supportive analysis, we will impute the worst possible 6MWT distance at 6 months as the component for primary hierarchical composite for all individuals who do not have this measurement, regardless of the reason. We will use the primary analytic method here and the analysis will be conducted in the ITT population only.

5.3.1.8 Supportive Analysis (Tipping Point) for Nonparametric Test of FCM vs. Placebo for Primary Composite

We will perform tipping point assessments to determine the sensitivity of the primary efficacy result to the missing 6 month 6MWT distance data. The tipping point analysis will assume progressively biased tie breaking. Hence, starting with all missing 6MWT values favouring the placebo to break the tie and checking if this does not change inference from the primary analyses. However, if it does change the inference then we will continue going down the scale to find the tipping point. This will be conducted in the ITT population only.

5.3.1.9 Supportive Analysis (Total burden of HF impact) for Nonparametric Test of FCM vs. Placebo for Primary Composite

To further understand the burden of the disease, we will analyse a combined endpoint of CV death and frequency of intervention for worsening heart failure (hospitalization or urgent heart failure visits), through the duration of the study. The analytic methods will follow that for the primary analyses. The analysis will be conducted in the ITT population only.

5.3.2 FCM vs. Placebo for Top Secondary Outcome

This analysis will compare time from randomization to the first occurrence of CV death or hospitalization for heart failure. The Cox proportional hazards model will be employed to conduct this comparison. The Cox model will include treatment, region as a stratification variable and will be adjusted for pre-decided baseline covariates as noted in section 4.1. The test will be two-tailed and will be performed at an overall α of 0.04. This analysis will be performed by the ITT principle based on randomized treatment assignment and we expect adequate power to detect a pre-specified relative risk reduction of 20%.

5.3.2.1 Supportive Analysis for FCM vs. Placebo for Top Secondary Outcome

As supportive analysis, time from randomization to the first occurrence of CV death or hospitalization for heart failure will be analysed in PP using the same approach as for the primary analysis based on the ITT population.

5.3.2.2 Sensitivity Analysis (Tipping Point) for FCM vs. Placebo for Top Secondary Outcome

In case there are 5% or more participants who prematurely discontinue from the study follow-up without having an event of death or hospitalization for heart failure, and the hazard ratio obtained from the top secondary outcome analysis is between 0.85 and 1.15 inclusive, we will perform tipping point assessments to determine the sensitivity of the result obtained from the top secondary analysis to the missing data caused by participants' early discontinuation. Events will be imputed during their missed follow-up time (i.e., time from early discontinuation to trial termination visit) under various scenarios for the hazard rates for the non-completers in each treatment arm. For each scenario, 20 imputations will be performed and the results will be combined across the 20 datasets that have both the actual events and imputed events using Rubin's rule (Rubin, 1987). Hazard ratio (95% CI) and p-value will be calculated for each scenario. The goal of this analysis is to find the scenarios where the top secondary outcome results conclusion could be changed. This analysis will be conducted in the ITT population only.

5.3.2.3 Sensitivity Analysis for Russia Ukraine War Impact (censor the data after invasion) for FCM vs. Placebo for Top Secondary Outcome

As one of the two sensitivity analyses to assess the impact of the Russia-Ukraine war on the top secondary outcome, we will censor the data from Russia and Ukraine for the time from randomization to the first occurrence of CV death or hospitalization for heart failure outcome with a date after invasion (24 February, 2022). The analytic method will the same as used for top secondary analysis. This will be conducted in the ITT population only.

5.3.2.4 Sensitivity Analysis for Russia Ukraine War Impact (exclude participants from these two countries) for FCM vs. Placebo for Top Secondary Outcome

As the second sensitivity method to assess the impact of the war on the top secondary outcome, we will exclude participants from Russia and Ukraine for comparison of the time from randomization to the first occurrence of CV death or hospitalization for heart failure outcome using the primary analytic method. This will be conducted in the ITT population only.

5.4 Subgroup Analyses for Top Secondary Outcome

Subgroup analyses will be performed for the top secondary outcome in the ITT population in order to explore whether treatment effects on the risk of developing CV events are consistent across subgroups. Subgroup analyses will be performed using the same analysis models as for the top secondary endpoints, with the addition of the subgroup factor and its interaction with treatment. The same subgroup analyses will also be repeated in the PP population.

The subgroups will be divided by categories for continuous variables. The subgroup analyses will be summarized via a forest plot and interaction p-values will be reported. We would look further into the subgroup if any interaction p-values are smaller than 0.15.
Pre-specified subgroups are detailed below.

Key Subgroups of Interest include split by:
Age (<65 vs >=65 years old),
NT-proBNP (<median vs >=median pg/mL),
NYHA class (I and II vs III and IV),
Heart failure etiology (Ischemic, Non-ischemic, Unknown),
Ejection fraction (<= median vs. > median),
Estimated glomerular filtration rate (<60 vs 60+ ml/min/1.73m^2),
Sex (Male/Female),
Ferritin-TSAT (<100 ferritin vs ferritin >=100-300 with TSAT<20%),
Chronic renal insufficiency (Yes/No),
Diabetes mellitus (Yes/No),
Iron deficiency anaemia (female and haemoglobin <12 g/dL or male and haemoglobin <13.5 g/dL, vs higher haemoglobin value for either sex),
BMI (<25, >=25 to <30, and >=30),
Region (North America, Europe (includes Russia and Georgia), Asia Pacific),
Race (White, Black, Other(American indian or Alaska native, Asian, multiple, native Hawaiian or other pacific islander, other)),
Atrial fibrillation (Yes/No),
Hospitalization for HF within past 12 months (Yes/No)

5.5 Secondary Outcomes

All other secondary outcomes are listed and defined below. These secondary outcomes will be tested in the order listed below and are considered as supportive in the assessment of the effect size attributable to FCM and will be analysed in ITT only and without a multiplicity adjustment.

(1) Mean change in 6MWT distance from baseline to 12 months will be compared using linear regression adjusting for baseline value of 6MWT distance and region. We will not adjust for other baseline covariates.

(2) Time to CV deaths or intervention for worsening heart failure (hospitalization or urgent heart failure visits) defined as time from randomization to the earliest of confirmed CV death or confirmed intervention for worsening heart failure will be compared using the Cox proportional hazards model.

(3) Time to CV deaths or CV hospitalizations defined as time from randomization to the earliest of confirmed CV death or confirmed CV hospitalization will be compared using the Cox proportional hazards model.

(4) Time to CV deaths defined as time from randomization to confirmed CV death (deaths confirmed as “Unknown” type will be included in the CV death counts) will be compared using the Cox proportional hazards model.

(5) Time to non-cardiovascular deaths defined as time from randomization to confirmed non-CV death will be compared using the Cox proportional hazards model.

(6) Time to first confirmed hospitalization for myocardial infarction (MI) defined as time from randomization to the earliest confirmed hospitalization for MI will be compared using the Cox proportional hazards model.

(7) Time to first confirmed hospitalization for stroke defined as time from randomization to the earliest confirmed hospitalization for stroke will be compared using the Cox proportional hazards model.

(8) Time to first confirmed hospitalization for other CV event defined as time from randomization to the earliest confirmed hospitalization for other CV event will be compared using the Cox proportional hazards model.

(9) Time to first confirmed urgent heart failure visit defined as time from randomization to the earliest confirmed urgent heart failure visit will be compared using the Cox proportional hazards model.

All time to event secondary outcomes will be analysed using the same approach as in the top secondary outcome analysis based on the ITT population. To assess change from baseline, a baseline measurement and the 12-month measurement both are required.

5.6 Hypophosphatemia Sub-study Analyses

A separate appendix to this SAP will detail analyses to be conducted in the Hypophosphatemia safety sub-study participants.

5.7 Exploratory Analyses

The below endpoints will be explored to further help interpret the primary analyses. All analyses will be conducted in ITT population only.

(1) Time to all cause death at one year defined as time from randomization to all cause death within 1 year (non-events censored at 1 year) will be compared using the Cox proportional hazards model.

(2) Number of heart failure hospitalizations at one year will be analysed using negative binomial regression analysis.

(3) Combination of all cause death and number of heart failure hospitalizations at one year will be analysed using the same method as used for the primary efficacy endpoint.

(4) Mean change in the 6MWT distance from baseline to six months will be compared using linear regression adjusting for baseline value of 6MWT distance and region. To assess change from baseline, a baseline measurement and the 6-month measurement both are required

(5) Time to all cause death through the duration of the study defined as time from randomization to all cause death (non-events censored at last known alive date) will be compared using the Cox proportional hazards model.

(6) Combination of CV death and total number of heart failure hospitalizations through the duration of the study will be analysed using the same method as used for the primary efficacy endpoint.

(7) Combination of CV death and total number of urgent heart failure visits through the duration of the study will be analysed using the same method as used for the primary efficacy endpoint.

(8) Combination of investigator-reported events of cardiovascular death and number of heart failure hospitalizations at 1 year and change in 6-minute walk distance (6MWD) at 6 months using the same method as for the primary efficacy endpoint.

(9) Time to first investigator-reported cardiovascular death or hospitalization for heart failure will be compared using the Cox proportional hazards model.

(10) Days alive and out of hospital (any cause) at 1 year as reported by investigator will be summarized overall and by region. It will be compared using a modified Poisson approach.

(11) Mean change in the 6MWT distance from baseline to 12 months will be compared using linear regression adjusting for baseline value of 6MWT distance and region in the subset of population with NYHA class of III/IV at baseline. To assess change from baseline, a baseline measurement and the 12-month measurement both are required

(12) Mean change in the 6MWT distance from baseline to 6 months will be compared using linear regression adjusting for baseline value of 6MWT distance and region in the subset of population with NYHA class of III/IV at baseline. To assess change from baseline, a baseline measurement and the 6-month measurement both are required

(13) Responder analyses for change in 6MWT distance from baseline to 6 months, where a change of 10 and 20 meters respectively is considered as a responder will be tested using chi-square test.

6 SAFETY ANALYSIS

There are no *a priori* hypotheses to be tested for safety. Safety will be assessed within the Safety population unless specified otherwise. Nominal visit-based Box and Whisker plots will be produced for continuous safety variables by randomized treatment where applicable. Shift tables for vital signs will be created for dosing days. Supplementary analyses will only be performed where these summaries suggest that there may be clinically significant differences.

For continuous safety parameters, at least one post-randomization measurement is required for inclusion in the analysis. To assess change from baseline, a baseline measurement is also required.

6.1 Adverse Events (AEs)

In the HEART-FID trial, any adverse experience (AE) that does not meet the definition of SAE is considered non-serious. Non-serious AEs will not be collected for this trial except for AEs leading to cessation of study medication administration. The original term used by investigators to identify non-serious AEs leading to discontinuation of study drug, or the SAEs, will be coded to the Preferred Term level using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment emergent adverse experiences (TEAE) are defined as those serious or non-serious adverse events that have a start date that is on or after the date of first study medication administration and on or before 30 days from the date of permanent drug discontinuation.

Similarly, treatment emergent serious adverse experiences (TESAE) are defined as those SAEs that have a start date on or after the date of first study medication administration and on or before 30 days from the date of permanent drug discontinuation. Events that have been determined as primary or secondary outcomes in the study are not regarded as SAEs for the safety analysis.

Summary of the following AEs will be provided by treatment group and by System Organ Class (SOC), Preferred Term (PT). These summaries will also be presented overall and by the subgroups of age, sex, race, and body mass index (BMI):

- All AEs (serious or non-serious resulting in discontinuation of study drug)
- All SAEs
- All TEAEs
- All TESAEs
- TEAEs (serious or non-serious) that result in discontinuation of study drug
- TESAEs considered related (possibly, probably or definitely) to study drug
- TESAEs with a fatal outcome.

We will also summarize severity, relatedness, seriousness criteria, and outcome at participant level for All TEAEs, the TEAEs categorized as below, all TESAEs, and All non-serious TEAEs.

TEAEs of Hypophosphatemia by SOC and PT
-MedDRA PT Blood phosphorus decreased
-MedDRA PT Blood phosphorus abnormal
-MedDRA PT Hypophosphataemia
-MedDRA LLT Hypophosphatemic rickets (or Hypophosphataemic rickets)
-MedDRA LLT Rickets familial hypophosphatemic (or Rickets familial hypophosphataemic)
-MedDRA PT Hypophosphatemia osteomalacia

TEAEs of Hypersensitivity/anaphylactoid reactions by SOC and PT
- MedDRA SMQ Anaphylactic reaction (narrow scope)
- MedDRA SMQ Angioedema (narrow scope)
- MedDRA PT of Hypersensitivity
- MedDRA PT of Type II hypersensitivity
- MedDRA PT of Serum sickness
- MedDRA PT of Serum sickness-like reaction
- MedDRA PT of Administration site vasculitis
- MedDRA PT of Type IV hypersensitivity reaction
- MedDRA PT of Stevens-Johnson syndrome
- MedDRA PT of Toxic epidermal necrolysis
- MedDRA Lower Level Term of Type III hypersensitivity reaction
- MedDRA Lower Level Term of Hemolytic anemia drug-induced
- MedDRA Lower Level Term of Haemolytic anaemia drug-induced
- MedDRA Lower Level Term of Immune hemolytic anemia drug-induced
- MedDRA Lower Level Term of Immune haemolytic anaemia drug-induced
- MedDRA Lower Level Term of Drug fever

TEAEs of Injection/infusion site reactions by SOC and PT
-MedDRA HLT Infusion site reactions
-MedDRA HLT Injection site reactions
-MedDRA HLT Administration site reactions NEC
-MedDRA PT Infusion related reaction
-MedDRA SOC of Skin and subcutaneous disorders with a PT of Skin discolourations

TEAEs of Medication error by SOC and PT

- MedDRA SMQ Medication errors (narrow scope)

TEAEs of Hemosiderosis by SOC and PT
-MedDRA PT Haemosiderosis
-MedDRA PT Haemotochromatosis
-MedDRA PT Iron overload
-MedDRA PT Hepatic siderosis
-MedDRA LLT Pulmonary siderosis
-MedDRA PT Pulmonary haemosiderosis
-MedDRA PT Superficial siderosis of central nervous system

We will also summarize any non-serious TEAEs occurring in 5 or more percent of participants in any treatment arm. Non-serious AEs as collected for this trial are defined at the beginning of the section.

6.2 Laboratory Data

- Descriptive statistics at baseline and at each scheduled (or reported) visit through 1 year along with the lowest observed value and the highest observed value will be provided for central laboratory measurements as identified below, and for changes from baseline by treatment. Shift tables will be provided for the max or min changes relative to baselines. Grades based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 or higher will be identified algorithmically where possible and as applicable for Haematology and Chemistry central laboratory data and they will be summarized by scheduled visit through 1 year using bar-chart and percentages. Any subjects with missing baseline values will not be included in change from baseline or shift tables
    a. Hematology: Hb, Hct, RBC, WBC, MCV, MCH, MCHC, RDW, platelets, differential count, and reticulocyte count
    b. Chemistry: Sodium, potassium, chloride, BUN, creatinine, eGFR (calculated using CKD-EPI formula), albumin, alkaline phosphatase, total bilirubin, GGT, AST, ALT, LDH, calcium, phosphorus, glucose, bicarbonate, serum glucose, albumin and magnesium
    c. Iron indices: Serum iron, serum ferritin, total iron binding capacity (TIBC), percentage serum transferrin saturation (TSAT), and Unsaturated Iron Binding capacity
    d. Other: 1,25 (OH)2 Vitamin D, 25 (OH) Vitamin D, Parathyroid Hormone as collected in sub-study participants, NT-proBNP

Additionally, Hb and iron indices laboratory data will be summarized in ITT population too.

6.3 Previous and Concomitant Medications and Interventions

Concomitant medications and interventions to be summarized for ITT and Safety. Baseline and post-baseline determination will be made programatically in reference to randomization date and assessment date(s).

- Concomitant medications of interest at baseline will be summarized by treatment.
- Post baseline concomitant medications of interest will be summarized by treatment.
- Post baseline concomitant intervention will be summarized by treatment.

6.4 Vitals and Physical Assessments

- Descriptive statistics and change from baseline by treatment at each scheduled visit will be provided through 1 year along with the worst observed value and the best observed value targeted physical exam results and vital signs (pre-dose, post-dose and

30 min post-dose) and: systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and BMI.

- Shift tables for Heart rate, SBP and DBP will be provided for the dosing days through 1 year. Baseline for these shift tables will be the pre-dosing value at the respective visit.

6.5 Drug Exposure

The following types of treatment durations will be calculated for FCM and placebo arm.

- Total treatment duration (including days off study drug) = Months between the first and last injection (last injection date – first injection date +1)/30.4375
- Total observation duration = Number of months in the study (date of final study disposition –date of randomization +1)/30.4375.

We will also summarize the total number of infusions received and cumulative dose by treatment for the participants.

Kaplan Meier estimates of time to permanent study drug discontinuation will be summarized by treatment.

Frequency rates of participants, who reach the improved iron indices threshold hemoglobin levels (i.e. participants whose dosing labs are outside the following levels: Hgb <13.5 g/dL(females) or <15.0 g/dL (males) and serum ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20% prior to any dosing visit will be presented by treatment. We will also summarize any participants whose treatment was switched due to improved iron indices through the study for FCM arm.

Summaries of duration of treatment, study drug interruption, and drug compliance will be provided by treatment through the overall study period in Safety Population.

6.6 Events of Special Interest related to HF that did not lead to Hospitalization

- All events of interest related to HF that did not lead to hospitalization collected in the study will be summarized by treatment. Specifically, the events are: supraventricular arrhythmia, ventricular arrhythmia, and renal failure, all requiring urgent/emergent intervention.

6.7 Hospitalizations not part of Primary and Secondary Outcomes

- All hospitalizations collected in the study that do not comprise primary or secondary outcomes (non-CV hospitalizations) will be summarized by treatment.

6.8 COVID-19 Related

Any deviations from the protocol related to COVID-19 will be summarized by treatment and a listing will be generated. Listings of all participants recorded as impacted by COVID-19 (related to visit completion, early study or treatment discontinuation, and any reported adverse events of COVID-19 as defined by MedDRA SMQ COVID-19 narrow scope) will also be provided, as appropriate.

6.9 Other Safety Assessments

All adverse events of special interest (ventricular tachycardia, supraventricular tachycardia, and renal failure, all requiring urgent/emergent intervention) will be summarized at participant level by treatment.
If participant or participant's partner becomes pregnant while on the study, the information will be included in the narratives and no separate table will be provided.

7 DATA SAFETY MONITORING BOARD AND INTERIM ANALYSES

7.1 Interim Analyses

The below text regarding interim analyses is as is written in the CSP 1VIT15043, version 3.0, 11 January 2021. The overall alpha levels to be used for primary and top secondary analyses are described in section 1.4.

A Data and Safety Monitoring Board (DSMB) Committee will review safety data, including a tally of the composite outcome events at least every 6 months. The DSMB can recommend stopping the study for safety concern at any point. In addition, one interim analysis is planned to determine if an early stopping for an overwhelming efficacy should be recommended or if an increase in sample size is warranted. The details as identified in Section 8.10 of the protocol are that this analysis will be conducted after 2250 (75%) participants have been randomized. Significance level will be set at 0.0001 for this analysis, resulting in an adjusted significance level for the final analysis of 0.0099 for the primary endpoint and 0.0499 for the first secondary endpoint, preserving the overall significance at 0.01 and 0.05, respectively. Conditional power will be estimated based on data accrued to date and presented to the DSMB.

The DSMB may recommend that the study continues as planned, discontinue the study, or that the trial be continued with recommended changes to the protocol.

The Executive Steering Committee will determine if an increase in sample size is warranted in order that at least 771 participants will experience an event of CV death or hospitalization for heart failure.

8 DATABASE SOURCES

The HEART-FID clinical database will be housed in RAVE Electronic Data Capture (EDC) hosted by Duke Clinical Research Institute (DCRI). In addition, DCRI and KCR will obtain protocol deviation from CTMS, the central laboratory data from Labcorp, and the CEC data from the DCRI CEC group. DCRI will obtain unblinded randomization data collected in the Interactive Web Response System (IXRS) from Almac after the database is locked at the end of the trial.

9 REFERENCES

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10 APPENDICES

Additional Appendices may be produced separately and finalised following finalisation of SAP but before database lock.

10.1 Appendix 1: Summary of Amendments to the Protocol relevant to the SAP are here. Details can be found within the CSP.

Protocol Version 2 and 3:

Affected Sections	Summary of Revisions
Appendix 1	Added a sub-study protocol to evaluate hypophosphatemia.
8.10 Stopping Rules and Interim Analysis	The DSMB may recommend that the study continues as planned, discontinue the study or that the trial be continued with recommended changes to the protocol. The Executive Steering Committee will determine if an increase in sample size is warranted in order that at least 771 participants will experience an event of cardiovascular death or hospitalization for heart failure.
4.5 Discontinuation from Study Drug	Added a definition for a participant permanently discontinued from the study.

10.2 **Appendix 2:** Simulations for power estimation for the primary endpoint were conducted at the time of writing the original version of the CSP. The below detailed information was used at the time.

Clinical Rationale: The proposed composite endpoint is intended to capture the clinical effects of the proposed treatment of participants in heart failure with reduced ejection fraction with iron deficiency with or without anemia. From a participant's and clinician's perspective, the essential elements are aimed towards improving the health and well-being of participants with disease as complex as heart failure with reduced ejection fraction. By targeting the experience of participants with heart failure as measured by survival, burden of heart failure hospitalizations, and functional status the proposed composite end-point reflects the key characteristics of a robust composite endpoint (Anker 2016). The rationale for including the burden of hospitalizations is based on the well-recognized problem that recurrent hospitalizations for worsening heart failure are a common occurrence in participants, and they impose a substantial clinical burden on participants and their families as indicative of worsening of their condition (Gheorghiade 2013). Despite the importance of repeat events, they are often ignored in the majority of clinical trials in favour of 'time to first event' analyses (Zannad 2013). In addition, heart failure is characterized as a disorder with significant functional impairment in physical activities. One of the most robust assessments of functional impairment that may be feasible on a large scale is the 6MWT (Forman 2012). This standardized assessment has been used to define functional status and stratify risk for participants in heart failure as well as other conditions such as pulmonary hypertension. The use of this hierarchical, composite endpoint will enable us to provide a more robust and clinically-meaningful classification of participants with heart failure with iron deficiency into those who have improved, remained unchanged, or have deteriorated based on survival, burden of hospitalizations with heart failure, and functional status as measured by the 6MWT distance.

Methods:
Each participant from the treatment arm gets compared with each participant from the control arm based on the 12-month experience to determine treatment response per the following hierarchy:

1. CV death

   If both die, the one who survives longer is better off;
   If one dies, the one that survives is better off;
   If neither dies, examine hospitalizations.

2. Hospitalization for worsening heart failure

   The one with fewer hospitalizations is better off;
   If number hospitalized equal (both not hospitalized, both with 1 hospitalization etc.), compare 6MWT;

3. Change in 6MWT

   The one with higher change in 6MWT is better off;

Statistical Test
The main comparison will be conducted using the Wilcoxon-Mann-Whitney test. The comparison of individuals in the treatment versus control arms is equivalent to ranking all individuals according to their experience. At one end of the ranking are individuals with the best experience - those alive and not hospitalized for worsening heart failure ordered according to their improvement in 6MWT; at the opposite end are those who die ordered according to their survival time. Those alive but hospitalized are in the middle, ordered according to their number

of hospitalizations for worsening heart failure and then by their change in 6MWT. The non-parametric Wilcoxon-Mann-Whitney test sums the ranks of those in the treatment arm and compares them with the sum of ranks in the control arm.

Table 10.2.1 Assumptions for Sample Size Calculations

Ranked tier at 12-month endpoint	Control	Treatment
Death total	8%	6.8%
Death without hospitalization	4%	3.4%
Death with hospitalization	4%	3.4%
Hospitalizations in survivors		
1	6%	4.8%
2	3%	2.4%
3 or more	1%	0.8%
Change in 6MWT	Mean = 0 SD = 90	Mean = 18 SD = 90
Empirical Power: 0.9500 (N=2930, α=0.0025) Clinically-Meaningful Difference: 0.068/0.08 = 0.85		

Conclusion
With 3000 participants (1500 per arm) and 2.5% annual loss to follow up, our simulations estimate ≥90% power at various two-sided significance levels between 0.0025 and 0.01.

10.3 Appendix 3: Ranking Algorithm (primary efficacy endpoint)

Scenario	Participant: i/j	All-cause Mortality (1 year)	Survival Times (from baseline)	Heart Failure hospitalization (1 year)	6 month change in 6MWT	Score
1	i	Dead	Low	not in consideration	not in consideration	-1
	j	Dead	High	not in consideration	not in consideration	+1
2	i	Dead	not in consideration	not in consideration	not in consideration	-1
	j	Alive	not in consideration	not in consideration	not in consideration	+1
3	i	Alive	not in consideration	High	not in consideration	-1
	j	Alive	not in consideration	Low	not in consideration	+1
4	i	Alive	not in consideration	Tied	Low	-1
	j	Alive	not in consideration	Tied	High	+1