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Reimbursement Review

Ferric Carboxymaltose (Ferinject)

Sponsor: CSL Vifor
Therapeutic area: Iron deficiency in adult patients with heart failure

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Clinical Review

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Abbreviations

6MWT	6-minute walk test
AHF	acute heart failure
AE	adverse event
CDA-AMC	Canada's Drug Agency
CHF	chronic heart failure
CI	confidence interval
CSS	clinical summary score
CV	cardiovascular
ESA	erythropoiesis-stimulating agent
FAS	full analysis set
FCM	ferric carboxymaltose
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HRQoL	health-related quality of life
ID	iron deficiency
IDA	iron deficiency anemia
KCCQ	Kansas City Cardiomyopathy Questionnaire
LOCF	last observation carried forward
LVEF	left ventricular ejection fraction
MID	minimal important difference
NYHA	New York Heart Association
OR	odds ratio
PGA	Physician's Global Assessment
PPS	per-protocol set
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SD	standard deviation
TEAE	treatment-emergent adverse event
TSAT	transferrin saturation

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Background Information of Application Submitted for Review

Item	Description
Drug product	FCM (Ferinject), 50 mg elemental iron/mL, vial for injection (2 mL, 10 mL, 20 mL)
Sponsor	CSL Vifor
Indication	For the treatment of ID in adult patients with heart failure and NYHA class II or class III to improve exercise capacity. The diagnosis of ID must be based on laboratory tests.
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	March 11, 2024
Recommended dose	The individual iron need for repletion using FCM is determined based on the patient's body weight and hemoglobin level. The maximum recommended cumulative dose of FCM is 1,000 mg of iron (20 mL FCM) per week. If the total iron need is higher, then the administration of an additional dose should be a minimum of 7 days apart from the first dose. A single FCM administration should not exceed either 15 mg iron/kg body weight, or 1,000 mg iron (20 mL FCM). Reassessment should be performed by the clinician based on the individual patient's condition. The Hemoglobinlevel should be reassessed no earlier than 4 weeks post final FCM administration to allow adequate time for erythropoiesis and iron utilization. In the event the patient requires further iron repletion, the iron need should be recalculated. In adult patients with chronic kidney disease who are hemodialysis-dependent, a single maximum daily dose of 200 mg of iron as FCM should not be exceeded.

FCM = ferric carboxymaltose; ID = iron deficiency; NOC = Notice of Compliance; NYHA = New York Heart Association.

Introduction

Heart failure (HF) is a complex and life-threatening syndrome in which abnormal heart function leads to subsequent risk of clinical symptoms and signs of reduced cardiac output and/or pulmonary or systemic congestion at rest or with stress. It is the third leading cause of hospitalization in Canada, with a median length of stay of 7 days, and leads to readmission in 1 of 5 patients within 30 days after discharge.[1,2] This condition is marked by significant morbidity and mortality, reduced functional capacity, and poor quality of life. Patients with chronic HF (CHF) require continuous medical care, frequent monitoring, hospitalizations, and extensive treatment.[3,4]

Symptoms of HF are classified using the New York Heart Association (NYHA) functional classes I to IV, which categorize the severity of symptoms ranging from minimal limitations during physical activity (class I) to severe symptoms even at rest (class IV). These symptoms reflect the progressive impact of HF on daily activities and quality of life.[5]

Approximately 60% of patients with HF have anemia and 40% of those without anemia have iron deficiency (ID).[4,6] When iron levels are too low to support adequate hemoglobin synthesis, it can lead to ID anemia

(IDA), which impairs the blood's ability to carry oxygen efficiently either due to a reduced number of red blood cells or low Hemoglobinlevels. While anemia can have various causes, ID is the most prevalent.[7] This condition significantly impacts patient well-being and outcomes[8,9] as iron plays a critical role in oxygen transport and cellular energy metabolism, particularly in tissues demanding high energy like cardiac muscle.[10-12]

ID can be characterized in 2 main ways: depleted iron stores due to insufficient dietary intake, impaired absorption, or chronic blood loss (absolute ID); and/or reduced circulating iron linked to chronic inflammation, particularly seen in cardiovascular (CV) diseases (functional ID).[13,14] This inflammation leads to an increased release of hepcidin, a liver-expressed type II acute-phase protein and a major player in iron homeostasis.[15] This mechanism contributes to ID observed in CV diseases. In HF, additional factors such as reduced bowel iron absorption due to generalized edema may also contribute to ID.[16,17] Therefore, hepcidin has been proposed as more a sensitive index to evaluate ID.[6,18,19]

The prevalence of ID is 35% to 55% in outpatients with HF and 72% to 83% in patients admitted to hospital due to HF.[20] A recent study in Alberta[21] found that among 17,463 patients with acute HF (AHF), 38.5% had their iron status evaluated within 30 days postindex episode, compared to 34.2% of 11,320 patients with CHF. Of those tested, 72.6% and 73.9% of patients with AHF and CHF, respectively, were found to have ID.

In addition to standard pharmacotherapy for HF with reduced ejection fraction (HFrEF), the Canadian Cardiovascular Society guidelines recommend assessing and treating ID in these patients.[4,22] Specifically, these guidelines advise considering IV iron therapy for patients with HF who meet all of the following criteria: an ejection fraction of 40% or less, and a serum ferritin concentration of less than 100 mcg/L or between 100 mcg/L to 299 mcg/L in combination with a transferrin saturation (TSAT) of less than 20%.[4,23]

Ferric carboxymaltose (FCM) is a colloidal dispersion which contains iron in a stable ferric state.[24] This complex consists of a polynuclear iron-hydroxide core bound to a carbohydrate ligand. It is specifically formulated to provide easily utilizable iron for the body's iron transport and storage proteins, namely transferrin and ferritin.[24]

FCM was approved by Health Canada with the following indications:[24]

- the treatment of IDA in adult and pediatric patients aged 1 year and older when oral iron preparations are not tolerated or are ineffective
- the treatment of ID in adult patients with HF and NYHA class II or class III to improve exercise capacity.

The diagnosis of ID must be based on laboratory tests. The sponsor request for reimbursement is as per the approved Health Canada indication. A Notice of Compliance was issued on March 11, 2024.

The dosage of FCM is expressed as mg of elemental iron, with each mL containing 50 mg of elemental iron.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to the call for input from Canada's Drug Agency (CDA-AMC) and from the clinical expert consulted by CDA-AMC for the purpose of this review.

Patient Input

No patient group input was submitted.

Clinician Input

Input From Clinical Expert Consulted by CDA-AMC

Treatment of ID with oral iron, although widely available and inexpensive, was described by the expert to be of limited utility due to poor absorption in general, but especially among patients with HF due to a variety of physiological factors specific to HF, such as epithelial dysfunction in the gut because of mucosal edema and reduced intestinal blood flow. The clinical expert indicated that IV iron is currently the preferred and guideline-recommended route for treatment of ID in patients with HF, and the intention of iron supplementation for ID in patients with HF is to improve health-related quality of life (HRQoL), functional capacity, and exercise capacity. The clinical expert described that IV iron formulations typically used in clinical practice include iron sucrose (maximum dose of 200 mg per sitting), ferric derisomaltose (maximum dose of 1,000 mg per injection), or FCM (maximum dose of 1,000 mg per week). Of the IV iron formulations, only FCM has a Health Canada–approved indication specific to the HF subpopulation; however, the other second-generation or third-generation IV iron formulations may also be used in clinical practice in this population.

The expert noted that guidelines[4,25-27] for the treatment of HF recommend all patients with HF should be tested for ID using serum ferritin and TSAT, and Canadian treatment guidelines recommend consideration of IV iron therapy for patients with HF with all of the following: left ventricular ejection fraction (LVEF) of 40% or less, and a serum ferritin of less than 100 mcg/L or between 100 mcg/L to 299 mcg/L in combination with a TSAT of less than 20%. The expert noted that based on Canadian and multiple international treatment guidelines for patients with HF and ID, patients with HF of any NYHA class may potentially be suitable for treatment with IV iron formulations, including FCM.

The clinical expert noted that most patients with HF receiving IV iron supplementation would be expected to continue this therapy for the duration of their lives. So long as guideline criteria for iron replacement therapy remain unchanged, and aside from intolerable adverse events (AEs) or patient or clinician decision or preference, there are no specific reasons to require discontinuation of FCM in a patient with HF and ID. According to the expert, there was no threshold of any laboratory parameter under which the drug should be discontinued due to lack of efficacy, and treatment should be required for as long as dictated by guideline criteria for ID-related IV iron replacement therapy.

IV iron formulations such as FCM are prescribed in hospital and can be ordered by any prescribing clinician managing the patient's HF and ID in that setting.

Clinician Group Input

A group of 13 independent clinical experts responding to the call for input from CDA-AMC gathered data from product monographs, literature, and personal experience. According to the group, ID is a progressive condition that can lead to IDA if untreated, affecting and impacting patients with HF by worsening disease symptoms and prognosis.

The clinician group emphasized that treatment goals include correcting hemoglobin deficits, replenishing iron stores, and maintaining them over time to alleviate symptoms and enhance HRQoL. While initial therapy often involves oral iron supplements, IV iron is recommended as the first-line treatment for patients with HF due to its rapid efficacy, especially because up to 50% of patients with HF can experience ID, leading to poorer functional capacity and increased hospitalizations and mortality. The clinician group noted that guidelines advocate for initiating IV iron therapy as soon as ID is identified.

The group noted challenges with previous IV iron formulations in Canada, requiring prolonged administration and lacking indications for use in pediatric populations or for the treatment of patients with ID and HF, underscoring the need for more efficient options. Newer products like FCM can deliver high doses (up to 1,000 mg) in a single session, potentially reducing treatment burden and improving adherence.

The clinician group indicated that treatment response is assessed using hematologic and iron parameters, aiming to normalize hemoglobin and ferritin levels. Clinically meaningful outcomes also include reducing the need for blood transfusions, alleviating symptoms, enhancing exercise capacity, improving quality of life, and reducing hospitalizations. Monitoring typically occurs 4 weeks to 8 weeks after completing the initial treatment course to track progress and adjust therapy as needed.

According to the input, factors to consider when deciding to discontinue treatment with FCM include postrepletion assessments of hemoglobin, ferritin, and TSAT levels. Treatment should be immediately discontinued in cases of hypersensitivity reactions or intolerance during administration, and it is contraindicated in patients with iron overload or persistent hypophosphatemia, where re-evaluation of treatment is warranted. FCM is appropriate for treatment in settings equipped to manage anaphylaxis and hypersensitivity reactions. It can also be administered in emergency departments or surgical inpatient units when indicated. While specialists like hematologists and other physicians commonly prescribe FCM, a specialist is not always required for diagnosis, treatment, and monitoring. Family medicine practitioners, as well as specialists in cardiology, gastroenterology, internal medicine, nephrology, and obstetrics and gynecology, among others, may also manage patients requiring IV iron therapy.

Drug Program Input

The drug programs provide input on each drug being reviewed by identifying issues that may affect their ability to implement a recommendation. For the review of FCM in adult patients with HF and ID, the drug plans provided questions or discussion points pertaining to relevant comparators, considerations for initiation, continuation, discontinuation, and prescribing of therapy, care provision issues, and system and economic issues (Table 6).

Clinical Evidence

Systematic Review

Description of Studies

The studies included were the FAIR-HF (N = 459), CONFIRM-HF (N = 304), and HEART-FID (N = 3,065) studies in patients with CHF, and the AFFIRM-AHF study (N = 1,132) in patients with AHF, all 4 of which are placebo-controlled, double-blind, randomized phase III (FAIR-HF and HEART-FID) or phase IV (CONFIRM-HF and AFFIRM-AHF) trials in adults with HF and ID. Of these, 2 studies (FAIR-HF and CONFIRM-HF) were focused primarily on clinical efficacy outcomes such as exercise capacity and NYHA class, while the remaining 2 studies (HEART-FID and AFFIRM-AHF) were focused primarily on composite outcomes related to hospitalizations and deaths. The studies ranged in duration from approximately 6 months (FAIR-HF) to 12 months (CONFIRM-HF, HEART-FID, and AFFIRM-AHF).

The 3 CHF studies each had a maximum allowed LVEF at screening or index visit, although the precise threshold varied: 40% or less (NYHA class II) or LVEF 45% or less (NYHA class III) in the FAIR-HF study, 45% or less in the CONFIRM-HF study, and 40% or less in the HEART-FID study (although historically reduced LVEF was also allowed given specific circumstances). In the AFFIRM-AHF study, the inclusion criteria required that patients had less than 50% LVEF within 12 months before randomization. All 4 included studies required serum ferritin to be less than 100 mcg/mL, or 100 mcg/mL to 299 mcg/mL or 100 mcg/mL to 300 mcg/mL with TSAT less than 20%. At baseline, mean patient ages were approximately 68 years to 71 years across the treatment groups, and the proportion of female patients ranged from 33% to 55%. All 4 studies included adult patients with NYHA class II or class III. Although the HEART-FID study also included NYHA class IV and the AFFIRM-AHF study included NYHA classes I and class IV, the overwhelming majority of patients belonged to NYHA class II or class III, with very few patients belonging to class IV (< 4% in the AFFIRM-AHF study and < 1% in the HEART-FID study) or class I (< 3% in the AFFIRM-AHF study). White race was disproportionately over-represented in all studies; 86% in the HEART-FID study, 95% in the AFFIRM-AHF study, and 99% to 100% in the FAIR-HF and CONFIRM-HF studies. Comorbidities were common, including hypertension, dyslipidemia, diabetes, atrial fibrillation, angina pectoris, and others.

Efficacy Results

NYHA Class

The NYHA functional class system is a subjective but widely used classification used to determine CHF severity based on symptoms, where NYHA class I suggests little to no symptoms of HF and class IV is defined by the inability to carry on any physical activity without discomfort and the presence of symptoms even at rest.

For the outcome of change in NYHA class from baseline, there was a benefit associated with FCM compared to placebo in the FAIR-HF study at week 24 (odds ratio [OR] = 2.400; 95% confidence interval [CI], 1.551 to 3.715; P < 0.001) where an OR of greater than 1 indicates a benefit of FCM, and in the CONFIRM-HF study at week 24 (OR = [redacted]; P = 0 0.004) and week 52 (OR = [redacted]; P < 0.001), where an OR of less than 1 indicates a benefit of FCM compared to

placebo. In the AFFIRM-AHF study, although the point estimate suggests benefit associated with FCM at week 52 based on an OR of greater than 1 (OR = [redacted]; P = 0.196), there was insufficient evidence to confirm a difference between the treatment arms because the 95% CI crossed the null. The HEART-FID study did not report this outcome.

6-Minute Walk Test

The 6-minute walk test (6MWT) is a common, validated test that measures the distance a patient can walk on a hard, flat surface over a 6-minute period under clinician supervision, where longer distances represent better exercise capacity. This outcome was assessed in the FAIR-HF, CONFIRM-HF, and HEART-FID studies, but not the AFFIRM-AHF study.

In the FAIR-HF study, the mean change from baseline in 6MWT at 24 weeks was [redacted] (standard deviation [SD] [redacted]) in the FCM group compared to [redacted] (SD [redacted]) in the placebo group, and the between-group difference was [redacted] (SD [redacted]) metres ([redacted]). Because no 95% CI was presented for the between-group results, additional data were requested from the sponsor, who provided a post hoc analysis of absolute differences on request to inform the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) analysis; according to these additional data, which may not follow the same analysis as described in the study's Statistical Analysis Plan, the between-group difference was [redacted] metres.

In the CONFIRM-HF study primary analysis at week 24, the change from baseline in 6MWT was [redacted] metres in the FCM and placebo groups, respectively. The least squares mean between-group difference was [redacted] (standard error [redacted].

In the HEART-FID study, as a component of the composite primary outcome, the mean change from baseline to 6 months (i.e., 24 weeks) in 6MWT was 8 metres (SD = 60) and 4 metres (SD = 59), respectively. Because no between-group differences were presented numerically, additional information was requested from the sponsor to support the GRADE analysis, which reported the following: the mean change from baseline to week 24 in 6MWT distance was [redacted] metres in the FCM group and [redacted] metres in the placebo group, with a between-group difference in change from baseline of [redacted] metres.

In the CONFIRM-HF study secondary analyses at week 52, the least squares mean between-group difference was [redacted] Sensitivity analyses using the per-protocol set (PPS) did not include reporting of between-group differences, but the within-group changes from baseline were similar to that of the full analysis set (FAS) analyses; the treatment benefit was also consistent across preplanned and post hoc subgroup analyses on demographic and disease-related features, and in a supportive analysis without primary imputation for deaths and hospitalizations.

In the HEART-FID study secondary analyses at week 52, the mean change was 5 metres (SD = 71) in the FCM group and 4 metres (SD = 72) in the placebo group. Between-group values were not reported numerically, so additional information was requested from the sponsor, in which it was reported that the

mean change from baseline to week 52 was [redacted] metres for the FCM and placebo groups, respectively, with a between-arm difference in change from baseline of [redacted] metres.

Kansas City Cardiomyopathy Questionnaire

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was reported in the FAIR-HF study (at 24 weeks), CONFIRM-HF study (at 24 weeks and 52 weeks), and AFFIRM-AHF study (at 24 weeks and 52 weeks) as a secondary outcome in each case. It is a 23-item, self-administered questionnaire that quantifies physical limitation, symptoms (stability, frequency, and burden), self-efficacy, social function, and HRQoL. Scores are transformed to a range of 0 to 100, where higher scores reflect better health status. Although studies have been performed assessing its measurement properties and validity, the KCCQ is primarily a clinical trial tool and is not typically used in real-world clinical practice.

In the FAIR-HF study at week 24, the study treatment effect of FCM was [redacted] greater in change from baseline of KCCQ overall summary score, compared to placebo ($P < 0.001$). Because there was no 95% CI provided with the point estimate for the FAIR-HF study, additional data were requested from the sponsor, which reported a between-group difference of [redacted] favouring FCM.

In the CONFIRM-HF study at week 24, the least squares mean between-group difference was [redacted] points. In the AFFIRM-AHF study, the difference was [redacted] In the CONFIRM-HF study at week 52, the between-group difference was [redacted] points, and in the AFFIRM-AHF study it was 1.44 (95% CI, –1.45 to 4.33; P not reported).

Fatigue Score

Only the CONFIRM-HF study assessed the change from baseline in fatigue score, ranked on a visual analogue scale from 0 to 10, where 0 implies no fatigue and 10 represents very severe fatigue. Some assessments of validity exist for this method of measuring fatigue, but there is no established minimal important difference (MID). At week 24 the between-group difference (as least squares mean) in change in fatigue score was [redacted], and at week 52 it was [redacted].

Serum Ferritin

At baseline, mean serum ferritin values were less than the threshold of 100 mcg/mL that defines ID in the context of HF in all included studies.

At week 24, across all studies, the FCM groups had mean serum ferritin levels of greater than 100 mcg/mL (although note that patients may still have “functional ID” if their TSAT is < 20% and their serum ferritin is 100 mcg/mL to 300 mcg/mL, as previously discussed), while the mean serum ferritin levels in the placebo groups were close to or less than 100 mcg/mL.

In the FAIR-HF study at week 24, the between-group difference in absolute mean serum ferritin was [redacted] in the FCM group and [redacted] in the placebo group ($P < 0.0001$).

In the CONFIRM-HF study, between-group values were not reported, but the mean serum ferritin at week 24 was [redacted] in the FCM group, representing a mean change from baseline of [redacted], and in the placebo group the mean serum ferritin was [redacted] representing a change from baseline of [redacted]. Additional data were provided by the sponsor upon request, in which it was reported that the between-group difference in change from baseline was [redacted] Numerical values for serum ferritin were not reported in the HEART-FID study, although graphical representation can be found in the supplementary documents. Additional data were provided by the sponsor upon request, in which it was reported that the between-group difference in change from baseline was [redacted] at week 24.

In the AFFIRM-AHF study, at week 24, the mean change from baseline was [redacted] in the FCM group compared to [redacted] in the placebo group; no between-group differences were reported. Additional data were provided by the sponsor upon request, in which it was reported that the between-group difference in change from baseline was [redacted] at week 24.

At week 52, the mean serum ferritin levels in the FCM groups of the CONFIRM-HF, HEART-FID, and AFFIRM-AHF studies were all in excess of 100 mcg/mL but were less than 300 mcg/mL. The FAIR-HF study was a 24-week study so there are no 52-week values. In the placebo groups, the levels were close to or less than 100 mcg/mL.

In the CONFIRM-HF study at 52 weeks, between-group values were not reported, but the mean serum ferritin in mcg/mL at week 52 in the FCM group was [redacted] representing a change from baseline of [redacted] and in the placebo group was [redacted] representing a change from baseline of [redacted] Additional data were provided by the sponsor upon request, in which it was reported that the between-group difference in change from baseline was [redacted] at week 52.

Values for serum ferritin were not reported in the HEART-FID study, although graphical representation can be found in the supplementary documents. Additional data were provided by the sponsor upon request, in which it was reported that the between-group difference in change from baseline was [redacted] at week 52.

In the AFFIRM-AHF study, at week 52, the mean change from baseline was [redacted] in the FCM group compared to [redacted] in the placebo group; no between-group differences were reported. Additional data were provided by the sponsor upon request, in which it was reported that the between-group difference in change from baseline was [redacted].

CV Hospitalizations

De novo analyses of CV hospitalization rate were provided by the sponsor upon request to assist in the review. Through both 26 weeks and 52 weeks, the between-group difference in event rate per 100 patient-years was lower in the FCM groups than the placebo groups. Through 26 weeks, the between-group difference in event rate per 100 patient-years for FCM versus placebo was [redacted] in the FAIR-HF study [redacted] in the CONFIRM-HF study, [redacted] in the HEART-FID study, and [redacted] in the AFFIRM-AHF study. Through week 52, the between-group differences were [redacted] in the CONFIRM-HF study, [redacted] in the HEART-FID study, and [redacted] in the AFFIRM-AHF study.

The HEART-FID and AFFIRM-AHF studies both had composite primary efficacy end points that included hospitalization-related outcomes; these will be discussed briefly here.

In the hierarchical composite primary end point of the HEART-FID study, death had occurred in 131 patients (8.6%) in the FCM group and in 158 (10.3%) in the placebo group at 12 months, there were 297 and 332 total hospitalizations for HF by 12 months, respectively, and the mean change in the 6-minute walk distance from baseline to 6 months was 8 metres (SD = 60) and 4 metres (SD = 59), respectively, (overall P = 0.02). The unmatched win ratio for the hierarchical composite outcome in the FCM group as compared with the placebo group was 1.10 (99% CI, 0.99 to 1.23). Results of prespecified sensitivity analyses that included different imputation methods were reported to be consistent with those of the primary analysis. Because more than half the patients underwent randomization after March 2020, the censoring of data after the onset of the COVID-19 pandemic would have excluded the majority of follow-up data from the analyses.

In the primary efficacy end point of the AFFIRM-AHF study, which was a composite of recurrent HF hospitalizations and CV deaths up to 52 weeks after randomization, the annualized event relative risk (RR) for FCM versus placebo was 0.79 (95% CI, 0.62 to 1.01; P = 0.059). In the prespecified COVID-19 sensitivity analysis, the annualized event RR for FCM versus placebo was 0.75 (95% CI, 0.59 to 0.96; P = 0.024).

CV Mortality

De novo analyses of CV mortality were provided by the sponsor upon request to assist in the review. Through both 26 weeks and 52 weeks, minor and inconsistent differences were observed, with 95% CIs that always crossed null. Through 26 weeks, between groups, the risk difference comparing FCM to placebo was [redacted] in the FAIR-HF study, [redacted] in the CONFIRM-HF study, [redacted] in the HEART-FID study, and [redacted] in the AFFIRM-AHF study. Through 52 weeks, the values were [redacted] in CONFIRM-HF, [redacted] in the HEART-FID study, and [redacted].

Harms Results

Adverse Events

In the FAIR-HF study the proportion of patients who experienced at least 1 AE was [redacted] in the FCM group and [redacted] in the placebo group, while in the CONFIRM-HF study the values were 79.6% and

75.7%, respectively. Overall AEs of any severity were not reported in the HEART-FID study. In the AFFIRM-AHF study, at least 1 AE was experienced by [redacted] patients in the FCM group and [redacted] patients in the placebo group.

Common AEs that occurred in at least 5% of any 1 treatment group across the FAIR-HF and CONFIRM-HF studies included cardiac failure, atrial fibrillation, angina pectoris, bronchitis, respiratory tract infection (viral), nasopharyngitis, influenza, increased blood pressure, hypertension, hypotension, headache, dizziness, and skin or subcutaneous tissue disorders. For the most part, the proportion of patients experiencing these events were relatively similar between treatment groups. Cardiac failure (chronic) appeared to be slightly less common in the FCM group than the placebo group (the FAIR-HF study: [redacted]; the CONFIRM-HF study: [redacted]). Common AEs that occurred in at least 5% of either treatment group in the AFFIRM-AHF study included cardiac failure, infections, gastrointestinal (GI) disorders, nervous system disorders, metabolism and nutrition disorders, renal and urinary disorders, vascular disorders, injury, and musculoskeletal disorders.

Serious Adverse Events

In the FAIR-HF study, a total of [redacted] in the FCM group and [redacted] in the placebo group reported at least 1 serious AE (SAE). The most common SAEs were cardiac disorders ([redacted] in the FCM and placebo groups, respectively).

In the CONFIRM-HF study, 43 patients (28.3%) in the FCM group and 53 patients (34.9%) in the placebo group reported at least 1 SAE. The most common SAEs were cardiac disorders ([redacted] in the FCM and placebo groups, respectively).

In the HEART-FID study, SAEs were reported in 581 patients (37.9%) in the FCM group and 537 patients (35.0%) in the placebo group. The most common SAEs during the treatment period were pneumonia, reported in 57 patients (3.7%) in the FCM group and 35 patients (2.3%) in the placebo group; acute kidney injury, reported in 46 patients (3.0%) in the FCM group and 40 patients (2.6%) in the placebo group; and COVID-19, reported in 39 patients (2.5%) in the FCM group and 37 patients (2.4%) in the placebo group. One event in the FCM group was classified as hypophosphatemia. This event resolved and FCM treatment was continued.

In the AFFIRM-AHF study, SAEs occurred in 250 (44.7%) of 559 patients in the FCM group and 282 (51.2%) of 551 patients in the placebo group. The most common were cardiac disorders ([redacted] in the FCM and placebo groups, respectively), followed by infections and infestations ([redacted] in the FCM and placebo groups, respectively), followed by general disorders and administration site conditions [redacted] in the FCM and placebo groups, respectively). Other SAEs were less common.

Withdrawals Due to AEs

In the FAIR-HF study, [redacted] in the FCM group and [redacted] in the placebo group withdrew from the study treatment due to AEs; in the CONFIRM-HF study, this occurred among [redacted] in the FCM group and [redacted] in the placebo

group; in the HEART-FID study, [redacted] and [redacted] and in the AFFIRM-AHF study, [redacted], respectively.

Deaths

In the FAIR-HF study, 5 deaths occurred in the FCM group ([redacted]) and 4 in the placebo group ([redacted] During the study period, [redacted] patients from the FCM group and [redacted] from the placebo group died. In the FCM group, 3 patients died due to sudden death, [redacted] due to ischemic stroke, and [redacted] due to severe anemia after terminating the study early. In the placebo group, [redacted] patients died due to myocardial infarction, pulmonary edema, and sudden death.

In the CONFIRM-HF study, a total of [redacted] in the FCM group and [redacted] in the placebo group died during the study period. The majority of deaths ([redacted]) were related to cardiac disorders and cardiac-related treatment-emergent AEs (TEAEs) in other system organ classes (e.g., sudden cardiac death and cardiac death in the category of general disorders and administration site conditions). Two patients in the placebo group died of noncardiac disorders (staphylococcal sepsis and acute renal failure).

In the HEART-FID study, death from any cause occurred in 361 patients (23.6%) in the FCM group and 376 patients (24.5%) in the placebo group (hazard ratio = 0.90; 95% CI, 0.78 to 1.05). The hazard ratio for death from any cause through month 12 was 0.82 (95% CI, 0.65 to 1.05). It is unknown how many deaths were due to AE.

In the AFFIRM-AHF study, [redacted] patients in the FCM group and [redacted] in the placebo group had TEAEs resulting in death. The majority of deaths were related to cardiac disorders and cardiac-related TEAEs in other organ classifications (e.g., sudden cardiac death and cardiac death in the category of general disorders and administration site conditions).

Notable Harms

Hypophosphatemia is a notable harm associated with FCM treatment that is not as highly associated with other IV iron formulations.

There were no reported cases of hypophosphatemia as TEAEs in both the FAIR-HF and CONFIRM-HF studies.

In the FAIR-HF study, transient decreases in phosphate levels were observed in the FCM group and this was reported to be most pronounced at week 4, but there were no clinical consequences, sequelae, or interventions associated with this change. Differences between treatment arms were observed in the percentage of patients with values outside the normal range for phosphate during follow-up ([redacted] in the FCM group versus [redacted] in the placebo group placebo; P = 0.008).

In the CONFIRM-HF study, the minimum recorded serum phosphorus value was [redacted] in 2 patients (1 in the FCM group and 1 in the placebo group), where hypophosphatemia is typically defined as less than 2.5 mg/dL. Among all patients, [redacted] experienced severe hypophosphatemia

based on the clinical events classification threshold of 0.3 mmol/L to less than 0.6 mmol/L, although the investigators did not report these as TEAEs.

The overall incidence of hypophosphatemia was not reported in the HEART-FID study, but 1 SAE of hypophosphatemia reportedly occurred in 1 patient in the FCM group and none in the placebo group. This hypophosphatemia event was considered by the investigator to be unrelated to FCM; the event resolved and FCM was continued.

In the AFFIRM-AHF study, there were [redacted] cases of hypophosphatemia reported, [redacted] of which was in the FCM group and [redacted] was in the placebo group.

Critical Appraisal

The overall risk of bias with regards to internal validity was low for the randomization process, allocation concealment, and maintenance of blinding.

Concerns for potentially important missing data were present for most outcomes assessed in at least 1 contributing study.

With regards to the outcomes assessed in this review, the primary efficacy analyses of the FAIR-HF (i.e., NYHA class) and CONFIRM-HF studies (i.e., 6MWT) were adjusted for multiplicity, but other outcomes from these studies were not.

In supportive analyses of the CONFIRM-HF study using the PPS instead of the FAS, the sample size was substantially reduced from the FAS due to a high number of protocol violations, especially in the active treatment arm, which may result in a risk of bias due to deviations from the intended interventions.

The external validity and applicability of the results of this review are limited by the absence of any direct or indirect evidence comparing FCM with other IV iron formulations, which are its direct comparators in patients with HF and ID despite having no specific indication in the HF population in Canada at this time. No conclusions can be drawn from any of the submitted evidence on the relative efficacy or safety of FCM with any other available IV iron formulation in patients with HF and ID. Additionally, there may be generalizability concerns regarding the demographics of the studies. The proportion of patients identified as white race was disproportionately high across the trials, particularly in the FAIR-HF and CONFIRM-HF studies (98% to 100% across the treatment arms) but this was also generally true in the other 2 studies (85% and 95%). The trials were primarily conducted in countries other than Canada, and so demographic features as well as clinical practice related to both ID and HF individually and together may differ. The HEART-FID study included US sites, but the other 3 included studies were conducted primarily in Eastern Europe with some sites in Western Europe, Oceania, Asia, and/or South America, and so the clinical practices and patient characteristics may differ from those in Canada. Additionally, the HEART-FID study was the most recently conducted study and had the most inconsistent results, especially with regards to 6MWT, when compared to the other included studies; the reason for this inconsistency is not certain, but it may be related to changes in clinical practice and standard of care over time.

The proposed reimbursement request in HF is specific to patients of NYHA class II or class III. However, this does not reflect the treatment guidelines, which do not specify any particular NYHA class in its recommendations for IV iron repletion therapies. The AFFIRM-AHF study enrolled patients with a broader range of NYHA classes (I to IV inclusive), and the HEART-FID study in patients with CHF also enrolled patients with NYHA class IV. However, the number of patients with NYHA class I and/or class IV was proportionally very low in both studies.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- HF disease severity as measured by NYHA score
- exercise capacity as measured by change in 6MWT from baseline
- HRQoL as measured using change from baseline in KCCQ
- fatigue score
- change from baseline in serum ferritin
- CV hospitalization rate
- CV mortality risk.

Table 2: Summary of Findings for FCM vs. PBO for Patients With CHF and ID

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
HF disease severity				
NYHA class Follow-up: 24 weeks	708 (2 RCTs)	**FAIR-HF (OR > 1 favours FCM)** • FCM, n = 294 • PBO, n = 150 • OR (95% CI) = 2.40 (1.55 to 3.72) **CONFIRM-HF (OR < 1 favours FCM)** • FCM, n = 132 • PBO, n = 132 • OR (95% CI) = [redacted]	Moderate[a,b,c,d]	FCM likely results in an improvement in NYHA class at 24 weeks when compared with PBO, although it is uncertain whether the magnitude of difference is clinically important.
NYHA class Follow-up: 52 weeks	248 (1 RCT)	**CONFIRM-HF (OR < 1 favours FCM)** • FCM, n = 127 • PBO, n = 121 • OR (95% CI) = [redacted]	Moderate[a,b,d]	FCM likely result in an improvement in NYHA class at 52 weeks when compared with PBO, although it is uncertain whether the magnitude of difference is clinically important.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Exercise capacity				
Change in 6MWT from baseline, mean metres (95% CI) Longer distances represent better exercise capacity MID: 15 metres Follow-up: 24 weeks	3,243 (3 RCTs)	**FAIR-HF** • FCM, n = 268: [redacted] • PBO, n = 134: [redacted] • Difference: [redacted] **CONFIRM-HF** • FCM, n = 130: [redacted] • PBO, n = 131: [redacted] • LSM difference: [redacted] **HEART-FID** • FCM, n = 1,282: [redacted] • PBO, n = 1,287: [redacted] • LSM difference: [redacted]	Very low[d,f,g]	The evidence is very uncertain about the effect of FCM on change in 6MWT from baseline when compared with PBO due to large unexplained inconsistency between the study results and imprecision.
Change in 6MWT from baseline, mean metres (95% CI) Longer distances represent better exercise capacity MID: 15 metres Follow-up: 52 weeks	2,495 (2 RCTs)	**CONFIRM-HF** • FCM, n = 125: [redacted] • PBO, n = 121: [redacted] • LSM difference: [redacted] **HEART-FID** • FCM, n = 1,140: [redacted] • PBO, n = 1,109: [redacted] • LSM difference: [redacted]	Very low[d,f,g]	The evidence is very uncertain about the effect of FCM on change in 6MWT from baseline when compared with PBO due to large unexplained inconsistency between the study results and imprecision.
Patient-reported outcomes				
Change in KCCQ overall summary score from baseline, mean score from 0 to 100 (95% CI) Higher score represents	690 (2 RCTs)	**FAIR-HF** • FCM, n = 286: [redacted] • PBO, n = 145: [redacted] • Difference: [redacted] **CONFIRM-HF**	Low[a,b,d,f]	FCM may result in an improvement in KCCQ overall summary score compared with PBO, but it is uncertain whether the magnitude of difference is clinically meaningful.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
better HRQoL Follow-up: 24 weeks		• FCM, n = 125: [redacted] • PBO, n = 124: [redacted] • LSM difference = 1.3 (–1.88 to 4.57)		
Change in KCCQ overall summary score from baseline, mean score from 0 to 100 (95% CI) Higher score represents better HRQoL Follow-up: 52 weeks	220 (1 RCT)	**CONFIRM-HF** • FCM, n = 114: [redacted] • PBO, n = 106: [redacted] • LSM difference = 4.5 (1.07 to 7.94)	Moderate[a,b,d]	FCM likely results in an improvement in KCCQ overall summary score compared with PBO, but it is uncertain whether the magnitude of difference is clinically meaningful.
Change in fatigue score, mean score from 1 to 10 (95% CI) Higher score represents more severe fatigue Follow-up: 24 weeks	241 (1 RCT)	**CONFIRM-HF** • FCM, n = 121: [redacted] • PBO, n = 120: [redacted] • LSM difference = –0.6 (–1.00 to –0.23)	Moderate[a,b,d]	FCM likely results in a decrease (improvement) in fatigue score when compared with PBO, but it is uncertain whether the magnitude of difference is clinically meaningful.
Change in fatigue score, mean score from 0 to 10 (95% CI) Higher score represents more severe fatigue Follow-up: 52 weeks	213 (1 RCT)	**CONFIRM-HF** • FCM, n = 110: [redacted] • PBO, n = 103: [redacted] • LSM difference = –0.7 (–1.07 to –0.25)	Moderate[a,b,d]	FCM likely results in a decrease (improvement) in fatigue score when compared with PBO, but it is uncertain whether the magnitude of difference is clinically meaningful.
Serum ferritin				
Change in serum ferritin from baseline, mean mcg/L (95% CI) Follow-up: 24 weeks	3,183 (3 RCTs)	**FAIR-HF** • FCM, n = 257: [redacted] • PBO, n = 113: [redacted] • Difference: [redacted]	Moderate[b,d]	FCM likely results in an increase (improvement) in serum ferritin when compared with PBO and there is uncertainty regarding the magnitude of effect.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		CONFIRM-HF • FCM, n = 124: [redacted] • PBO, n = 123: [redacted] • Difference: [redacted] **HEART-FID** • FCM, n = 1,279: [redacted] • PBO, n = 1,287: [redacted] • Difference: [redacted]		
Change in serum ferritin from baseline, mean mcg/L (95% CI) Follow-up: 52 weeks	2,603 (2 RCTs)	**CONFIRM-HF** • FCM, n = 114: [redacted] • PBO, n = 106: [redacted] • Difference: [redacted] **HEART-FID** • FCM, n = 1,142: [redacted] • PBO, n = 1,127: [redacted] • Difference: [redacted]	Moderate[b,d]	FCM likely results in an increase (improvement) in serum ferritin when compared with PBO and there is uncertainty regarding the magnitude of effect.
CV hospitalization				
Hospitalization due to any CV reason, event rate per 100 patient-years (95% CI)[i] Follow-up: 26 weeks	3,825 (3 RCTs)	**FAIR-HF** • FCM, n = 304: [redacted] • PBO, n = 155: [redacted] • Difference: [redacted] **CONFIRM-HF** • FCM, n = 150: [redacted] • PBO, n = 151: [redacted] • Difference: [redacted] **HEART-FID**	Moderate[b,d]	FCM likely results in a decrease (improvement) in annualized hospitalization rate per 100 patient-years when compared with PBO, although it is uncertain whether the magnitude of difference is clinically meaningful. A longer follow-up duration may be more informative for this outcome.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• FCM, n = 1,532: [redacted] • PBO, n = 1,533: [redacted] • Difference: [redacted]		
Hospitalization due to any CV reason, event rate per 100 patient-years (95% CI)[i] Follow-up: 52 weeks	3,366 (2 RCTs)	**CONFIRM-HF** • FCM, n = 150: [redacted] • PBO, n = 151: [redacted] • Difference: [redacted] **HEART-FID** • FCM, n = 1,532: [redacted][e] • PBO, n = 1,533: [redacted][e] • Difference: [redacted]	Moderate[b,d]	FCM likely results in a decrease (improvement) in annualized hospitalization rate per 100 patient-years when compared with PBO, although it is uncertain whether the magnitude of difference is clinically meaningful. A longer follow-up duration may be more informative for this outcome.
CV mortality				
Mortality due to any CV reason, risk difference (95% CI) Follow-up: 26 weeks	3,825 (3 RCTs)	**FAIR-HF** • FCM: [redacted] of 304 died[e] • PBO: [redacted] of 155 died[e] • Risk difference [redacted][e,j] **CONFIRM-HF** • FCM [redacted] of 150 died[e] • PBO: [redacted] of 151 died[e] • Risk difference: [redacted][e,j] **HEART-FID** • FCM [redacted] of 1,532 died[e] • PBO: [redacted] of 1,533 died[e] • Risk difference: [redacted][e,j]	Low[b,g,k]	FCM may result in little to no difference in CV mortality when compared with PBO at 26 weeks, but the duration of follow-up available may be insufficient to fully evaluate this outcome.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Mortality due to any CV reason, risk difference (95% CI) Follow-up: 52 weeks	3,366 (2 RCTs)	**CONFIRM-HF** • FCM: [redacted] of 150 died[e] • PBO: [redacted] of 151 died[e] • Risk difference [redacted] [redacted][e,j] **HEART-FID** • FCM: [redacted] of 1,532 died[e] • PBO: [redacted] of 1,533 died[e] • Risk difference: [redacted] [redacted][e,j]	Low[b,g,k]	FCM may result in little to no difference in CV mortality when compared with PBO at 52 weeks, but the duration of follow-up available may be insufficient to fully evaluate this outcome.

6MWT = 6-minute walk test; CHF = chronic heart failure; CI = confidence interval; CV = cardiovascular; FCM = ferric carboxymaltose; HF = heart failure; HRQoL = health-related quality of life; KCCQ = Kansas City Cardiomyopathy Questionnaire; LSM = least squares mean; MID = minimal important difference; NYHA = New York Heart Association; OR = odds ratio; PBO = placebo; RCT = randomized controlled trial; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]This outcome is subjective, but there was no suspected risk of bias due to adequate maintenance of blinding.

[b]No known MID so the target of certainty appraisal was any effect.

[c]Only the FAIR-HF study adjusted for multiplicity for this outcome (NYHA). With that exception noted, no studies adjusted for multiplicity for this or any other outcome in this table.

[d]Rated down 1 level for risk of bias due to missing data.

[e]This value was provided by the sponsor upon request to assist in the interpretation of the evidence. Note that the analysis is post hoc and not necessarily represented in the Statistical Analysis Plan of the relevant study.

[f]Rated down 2 levels for very serious inconsistency due to differences in magnitude of effect between the studies, wherein the 95% CIs of some studies are minimally overlapping or not overlapping.

[g]Rated down 1 level for serious imprecision. CI crosses thresholds between 1 set of: harm, no difference, or benefit.

[h]Although the CI could be rated down twice, it was judged to be a narrow CI and not a sufficient cause for concern.

[i]The total number of events for all patients in the treatment group was divided by the total patient-years of follow-up in that treatment group multiplied by 100. Follow-up duration is equal to time on study. Time on study (weeks) = (last known date – randomization date + 1)/7.

[j]Risk difference is FCM – placebo with 95% Miettinen-Nurminen CI.

[k]Rated down 1 level for indirectness. Based on clinical expert opinion, the duration of assessment is likely insufficient to identify a difference between treatment groups for this outcome.

Sources: Additional information request for absolute differences results data,[28] Clinical Study Reports for the FAIR-HF[29] and CONFIRM-HF studies,[30] and publication and supplementary appendix of the HEART-FID study.[31]

Table 3: Summary of Findings for FCM vs. PBO for Patients With AHF and ID

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
HF disease severity				
NYHA class, adjusted for baseline value Follow-up: 52 weeks	912 (1 RCT)	**AFFIRM-AHF (OR > 1 favours FCM)** [redacted]	Moderate[a,b,c,d]	FCM likely results an improvement in NYHA class at 52 weeks when compared with PBO in adult patients with AHF and ID, although it is

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
				uncertain whether the magnitude of difference is clinically important.
Exercise capacity				
6MWT	NA	NA	NA	There were no data available to inform this outcome in patients with AHF and ID.
Patient-reported outcomes				
Change in KCCQ overall summary score from baseline, mean score from 0 to 100 (95% CI) Higher score represents better HRQoL Follow-up: 24 weeks	835 (1 RCT)	**AFFIRM-AHF** • FCM, n = 422: [redacted] • PBO, n = 413: [redacted] • Difference (95% CI): [redacted]	Moderate[a,b,c,d]	FCM likely results in an improvement in KCCQ overall summary score when compared with PBO in adult patients with AHF and ID, although it is uncertain whether the magnitude of difference is clinically important.
Change in KCCQ overall summary score from baseline, mean score from 0 to 100 (95% CI) Higher score represents better HRQoL Follow-up: 52 weeks	738 (1 RCT)	**AFFIRM-AHF** • FCM, n = 368: [redacted] • PBO, n = 370: [redacted] • Difference (95% CI): [redacted][e]	Low[a,b,c,d,f]	FCM may result in an improvement in KCCQ overall summary score when compared with PBO in adult patients with AHF and ID, although it is uncertain whether the magnitude of difference is clinically important.
Fatigue	NA	NA	NA	There were no data available to inform this outcome in patients with AHF and ID.
Serum ferritin				
Change in serum ferritin from baseline, mean mcg/L Follow-up: 24 weeks	838 (1 RCT)	**AFFIRM-AHF** • FCM, n = 420: [redacted] • PBO, n = 418: [redacted] • Difference (95% CI): [redacted]	Moderate[b,c,d]	FCM likely results an increase (improvement) in serum ferritin when compared with PBO.
Change in serum ferritin from baseline, mean mcg/L	685 (1 RCT)	**AFFIRM-AHF** • FCM, n = 339: [redacted] • PBO, n = 346: [redacted]	Moderate[b,c,d]	FCM likely results in an increase (improvement) in serum ferritin when compared with PBO.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Follow-up: 52 weeks		• Difference (95% CI):		
CV hospitalization				
Hospitalization rate due to any CV reason, event rate per 100 patient-years (95% CI) Follow-up: 26 weeks	1,108 (1 RCT)	**AFFIRM-AHF** • FCM, n = 558: [e] • PBO, n = 550: [e] • Difference (95% CI): [e,g]	Moderate[b,c,d]	FCM results in a decrease (improvement) in hospitalization rate due to any CV reason when compared with PBO, although it is uncertain whether the magnitude of difference is clinically meaningful. A longer follow-up duration may be more informative for this outcome.
Hospitalization due to any CV reason, event rate per 100 patient-years (95% CI) Follow-up: 52 weeks	1,108 (1 RCT)	**AFFIRM-AHF** • FCM, n = 558: [e] • PBO, n = 550: [e] • Difference (95% CI): [e,f]	Moderate[b,c,d]	FCM results in a decrease (improvement) in hospitalization rate when compared with PBO in adult patients with AHF and ID, although it is uncertain whether the magnitude of difference is clinically meaningful. A longer follow-up duration may be more informative for this outcome.
CV mortality				
Mortality due to any CV reason, risk difference Follow-up: 26 weeks	1,108 (1 RCT)	**AFFIRM-AHF** • FCM: per 100[e] • PBO: per 100[e] • Risk difference: fewer per 100 (more per 100)[e,h]	Low[b,c,f,i,j]	FCM may result in little to no difference in CV mortality when compared with PBO at 26 weeks, but the duration of follow-up available may be insufficient to fully evaluate this outcome.
Mortality due to any CV reason Follow-up: 52 weeks	1,108 (1 RCT)	**AFFIRM-AHF** • FCM: per 100[e] • PBO: per 100[e] • Risk difference: fewer per 100 (more per 100)[e,h]	Low[b,c,f,i,j]	FCM may result in little to no difference in CV mortality when compared with PBO at 52 weeks, but the duration of follow-up available may be insufficient to fully evaluate this outcome.

6MWT = 6-minute walk test; AHF = acute heart failure; CI = confidence interval; CV = cardiovascular; FCM = ferric carboxymaltose; HF = heart failure; HRQoL = health-related quality of life; ID = iron deficiency; KCCQ = Kansas City Cardiomyopathy Questionnaire; MID = minimal important difference; NA = not applicable; NYHA = New York Heart Association; OR = odds ratio; PBO = placebo; RCT = randomized controlled trial; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]Rated down 1 for serious risk of bias caused by a high proportion of potentially important missing data.

[b]This outcome was not adjusted for multiplicity.

[c]No known MID so the target of certainty appraisal was any effect.

[d]Rated down 1 level for risk of bias due to missing data.

[e]This value was provided by the sponsor upon request to assist in the interpretation of the evidence. If this value represents an analysis outcome, note that the analysis is post hoc and not necessarily represented in the Statistical Analysis Plan of the relevant study.

[f]Rated down 1 level for serious imprecision. No known MID so target of certainty appraisal was any effect.

[g]The total number of events for all patients in the treatment group was divided by the total patient-years of follow-up in that treatment group multiplied by 100. Follow-up duration is equal to time on study. Time on study (weeks) = (last known date – randomization date + 1)/7.

[h]Risk difference is FCM – placebo with 95% Miettinen-Nurminen CI.

[i]Rated down 1 level for indirectness. Based on clinical expert opinion, the duration of assessment is likely insufficient to identify a difference between treatment groups for this outcome.

[j]Although the CI includes possibility of both benefit and arm, the CI is relatively narrow around the null, so it was subjectively judged that this was not imprecise enough to warrant rating down a second time for imprecision.

Sources: Additional information request for absolute differences results data,[28] and Clinical Study Report of the AFFIRM-AHF study.[32]

Long-Term Extension Studies

No long-term extension studies were submitted for this indication.

Indirect Comparisons

No indirect comparisons were submitted for this indication.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps in the evidence were summarized from the systematic review for this indication. The characteristics of some additional studies are briefly summarized in Appendix 1 as they were considered unlikely to impact the conclusions of the review, but are relevant to the indication under consideration. The sponsor also submitted a meta-analysis by Ponikowski and colleagues (2023)[33] which is summarized and critically appraised in the following.

Summary and Critical Appraisal of Meta-Analysis by Ponikowski and Colleagues (2023)[33]

Objective

The objective of the meta-analysis was to evaluate the effects of FCM treatment on clinical events, such as hospitalizations and mortality, in patients with HF and ID using patient-level data from randomized, placebo-controlled trials of FCM that enrolled adults with HF and ID.

Methods

Inclusion Criteria

Ponikowski and colleagues performed a pooled analysis of patient-level data from trials that met the following criteria: studied adult patients with HF and ID (defined as ferritin < 100 mcg/mL or ferritin 100 mcg/mL to 300 mcg/mL and TSAT < 20%); used FCM as an active treatment for ID; were double-blind, randomized, and placebo-controlled; had at least 52 weeks of follow-up; and prospectively recorded clinical outcomes (e.g., first and recurrent HF and CV hospitalizations, CV death, and all-cause death).

Included Studies

The meta-analysis ultimately included the CONFIRM-HF, AFFIRM-AHF, and HEART-FID studies. Searches were conducted to identify any additional studies, but none were added per the eligibility criteria. The authors were able to access individual patient data for the included studies.

End Points

The prespecified co-primary efficacy end points were:

- a composite of recurrent (total) CV hospitalizations and death for any CV reason (CV death)
- a composite of recurrent (total) HF hospitalizations and CV death.

All of these outcomes were based on events adjudicated independently by blinded event committees. All 3 FCM trials used consistent criteria for adjudication, which were prespecified in each trial.

The key secondary efficacy end points were: time to first CV hospitalization or CV death, time to first HF hospitalization or CV death, rate of total HF hospitalizations, time to first HF hospitalization, time to CV death, time to all-cause death, total CV hospitalizations, time to CV death, time to all-cause death, total CV hospitalizations, time to first CV hospitalization, and total all-cause hospitalizations.

All primary and key secondary end points were examined through 52 weeks of follow-up (primary end points were set with a time window up to 408 days).

Data Analysis

Efficacy analyses were conducted on the full analysis population defined as all randomly assigned patients who received at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment. The safety population comprised all patients who were randomly assigned and received at least 1 dose of study medication, and was used to assess baseline characteristics and analyze the frequency of AEs.

A negative binomial regression model was used to analyze event rates, including recurrent hospitalizations. The models were adjusted for baseline hemoglobin and region as fixed effects. Study was included as a random effect. The between-trial heterogeneity was explored by including a treatment by study interaction and a Cochrane Q test. Time-to-event outcomes used Cox proportional hazard analyses and the models were adjusted for hemoglobin at baseline and region. To explore between-trial heterogeneity, the study effect was included as a fixed effect.

Several preplanned subgroup analyses and sensitivity analyses were conducted. As the purpose of the sponsor presenting this meta-analysis was in part to discuss the impact of TSAT on efficacy results, the TSAT subgroup will be discussed briefly in this subgroup, but other subgroups will not be.

A sensitivity analysis incorporating the IRONMAN trial (which did not include FCM) was also conducted to evaluate IV iron formulations versus placebo, which will not be discussed in depth here. An additional sensitivity analysis was also conducted using all available follow-up data (i.e., beyond 52 weeks).

Results

Efficacy

The results were in favour of FCM without the 95% CI overlapping null for the co-primary composite end point of CV death and total CV hospitalizations (rate ratio = 0.86; 95% CI, 0.75 to 0.98; P = 0.029). Similarly FCM was associated with a 17% relative rate reduction in total CV hospitalizations (rate ratio = 0.83; 95%

CI, 0.73 to 0.96; P = 0.009) and a 16% relative rate reduction in total HF hospitalizations (rate ratio = 0.84; 95% CI, 0.71 to 0.98; P = 0.025). For the outcome of total HF hospitalizations and CV death, the result was in favour of FCM; however, the 95% CI overlapped null (0.75 to 1.01). For the outcome of time to CV death, the 95% CI also crossed null, indicating that there was no statistically significant difference between the treatment arms. Similarly, there was no statistically significant difference for time to all-cause death. Rate reductions in the primary composite end points were mainly driven by the treatment effect on HF hospitalizations and CV hospitalizations, with no apparent effect on CV or all-cause mortality.

In terms of subgroup results, there was a significant interaction effect identified between TSAT tertile and the composite of CV hospitalization and CV death (interaction P = 0.019) and between TSAT tertile and CV death (interaction P = 0.035), where patients in a lower TSAT tertile were more likely to see treatment benefit than those in a higher TSAT tertile. Although not statistically significant, a similar pattern was observed for the effect of TSAT on total HF hospitalizations and CV death (interaction P = 0.095). There were some other subgroups identified regarding “numerically” different treatment effects by subgroup (e.g., across hemoglobin tertiles and HF etiology); other than these, the effects of FCM therapy on both of the primary efficacy end points, CV death and all-cause death, were similar across other subgroups examined.

Safety

The incidences of investigator-reported serious TEAEs, serious TEAEs leading to death, and serious TEAEs leading to study discontinuation were similar across treatment groups through week 52. No deaths were judged to be the cause of serious treatment-related TEAEs. The rate of serious treatment-emergent infections was 9.9 per 100 patient-years and 9.6 per 100 patient-years in the FCM and placebo groups, respectively. Treatment appeared to be safe and well tolerated.

Critical Appraisal

The meta-analysis appears to be conducted appropriately. All of the included trials were placebo-controlled, double-blind, randomized phase III or phase IV trials in adults with HF and ID. The CONFIRM-HF study was focused on clinical efficacy outcomes such as exercise capacity and NYHA class, although the study did report survival and HF or CV-related outcomes as well. The AFFIRM-AHF and HEART-FID studies were focused primarily on composite outcomes related to hospitalizations and death. All 3 trials were at least 12 months in duration. The studies differed in minor ways with regards to inclusion criteria, such as whether NYHA class I or class IV was included; in the CONFIRM-HF study, only class II and class III were included, while the HEART-FID study additionally included class IV and the AFFIRM-AHF study did not specify any exclusions based on NYHA class. This was not expected to represent an important difference in patient populations, in part because prescription of IV iron is not dependent on NYHA class and in part because very few patients outside of class II and class III were included in any study overall. There were also minor differences with regards to the upper limit of LVEF and the range of included hemoglobin levels, but altogether these were considered very similar. The definitions of ID were the same across the studies.

A key difference in study design is that the AFFIRM-AHF study required patients to be hospitalized for AHF during enrolment, while the CONFIRM-HF and HEART-FID studies required a hospitalization within the prior year (or, in the case of the HEART-FID study, hospitalization within the prior 12 months

or elevated N-terminal pro-brain natriuretic peptide within 90 days of randomization). These differences are important to consider when interpreting the results but were not expected to pose a concern with regards to conducting a meta-analysis such as that presented in Ponikowski and colleagues (2023), and all of the studies do represent the patient population in question. The inclusion of the AFFIRM-AHF study, which involves hospitalized patients with AHF, introduces a significant between-trial difference in design and patient population. However, the HEART-FID study is a substantially larger trial, so any skewing of results due to the more at-risk population in the AFFIRM-AHF study may not be substantial. A sensitivity analysis excluding the AFFIRM-AHF study could have been useful to address this difference in patient population. Despite this minor concern, the treatment effect in the AFFIRM-AHF study was not consistently the highest in magnitude. In fact, the CONFIRM-HF study generally showed the largest treatment effect but also had the widest 95% CIs across all co-primary composite outcomes and their components. Further exploration into this observation may be warranted, but it does not discredit the meta-analysis results. In the publication, between-trial heterogeneity in treatment effect was explored and models were adjusted for baseline hemoglobin and region, which was considered appropriate. The study authors state that there was no identified heterogeneity between the trials for any primary or key secondary outcomes, and that the treatment arms appeared to be balanced by demographics.

Conclusions

Findings from 3 randomized controlled trials (RCTs) in CHF and 1 RCT in AHF demonstrated potential benefit of FCM compared to placebo in patients with HF and ID based on 24-week and 52-week outcomes. Evidence from 3 CHF studies, considered together, demonstrated that treatment with FCM likely results in an improvement in NYHA class at 24 weeks and 52 weeks, KCCQ at 52 weeks, fatigue score at 24 weeks and 52 weeks, and serum ferritin at 24 weeks and 52 weeks. There is uncertainty regarding whether the magnitude of benefit is clinically meaningful for all of the aforementioned outcomes. Treatment with FCM in patients with CHF may also result in an improvement in KCCQ at 24 weeks but the certainty was lower at this time point due to imprecision. In CHF, the evidence was very uncertain with regards to the effect of FCM on 6MWT at 24 weeks or 52 weeks due to inconsistency, imprecision, and missing data; notably, older studies (FAIR-HF and CONFIRM-HF) showed likely clinically meaningful benefit while a more recent and larger study (HEART-FID) did not show an important benefit, and the reason for this discrepancy is not fully clear. FCM may result in little to no difference in CV mortality when compared to placebo at 26 weeks or 52 weeks, but the duration of follow-up may be inadequate and studies may be inadequately powered to assess this outcome fully.

Evidence from 1 AHF study demonstrated that FCM likely results in an improvement in NYHA class at 24 weeks and 52 weeks, KCCQ at 24 weeks, and serum ferritin at 24 weeks and 52 weeks, CV hospitalization rate at 24 weeks and 52 weeks, and may result in little to no difference in CV mortality at 24 weeks or 52 weeks. There was uncertainty regarding whether the magnitude of effect observed was clinically meaningful for all of the aforementioned outcomes. There were no data available to inform the effect of FCM on 6MWT or fatigue in patients with AHF.

FCM was well tolerated in all included studies. The frequency of AEs was generally similar between treatment groups within each included study, where reported. These trends align with the expected pathophysiology of HF and ID and the expected treatment effect and side effects of iron supplementation. There were slightly more patients who experienced SAEs in the placebo groups than the FCM groups, and these were most commonly cardiac disorders. FCM is associated with a risk of hypophosphatemia, as detailed in the product monograph, and these events appeared relatively uncommon in the included studies in all treatment groups.

Other IV formulations of iron supplementation exist and are used in clinical practice to treat patients with HF and ID, albeit without a specific indication for this population. There is a lack of direct or indirect evidence comparing FCM to other third-generation or second-generation IV iron formulations, which represent the direct comparators of FCM. According to clinical practice guidelines in Canada and around the world, as well as clinical expert input, IV iron is standard of care for patients with HF and ID to improve exercise capacity and symptoms. The treatment goal of IV iron is not necessarily to improve hospitalization and mortality directly as these are likely more strongly driven by the patient's underlying HF, which is not modified by iron supplementation. Although FCM was demonstrated to be reasonably effective and safe compared to placebo, no conclusions can be drawn regarding the relative efficacy and safety of FCM with other commonly used IV iron formulations such as iron sucrose or ferric derisomaltose in the HF population.

Introduction

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of FCM for IV administration in the treatment of ID in adult patients with HF to improve exercise capacity.

Disease Background

Contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following have been summarized and validated by the CDA-AMC review team.

HF is a complex and life-threatening syndrome in which abnormal heart function leads to or increases clinical symptoms and signs of reduced cardiac output and/or pulmonary or systemic congestion at rest or with stress. It is the third leading cause of hospitalization in Canada, with a median length of stay of 7 days, and leads to readmission in 1 in 5 patients within 30 days after discharge.[1,2] This condition is marked by significant morbidity and mortality, reduced functional capacity, and poor quality of life. Patients with CHF require continuous medical care, frequent monitoring, hospitalizations, and extensive treatment.[3,4]

Symptoms of HF are classified using the NYHA functional classes I to IV, which categorize the severity of symptoms ranging from minimal limitations during physical activity (class I) to severe symptoms even at rest (class IV). These symptoms include fatigue, shortness of breath, swelling (edema), and reduced exercise tolerance, reflecting the progressive impact of HF on daily activities and quality of life.[5]

Approximately 60% of patients with HF have anemia and 40% of those without anemia have ID.[4,6] This condition significantly impacts patient well-being[8,9] as iron plays a critical role in oxygen transport and cellular energy metabolism, particularly in tissues demanding high energy like cardiac muscle.[10-12]

ID can be characterized in 2 main ways: depleted iron stores due to insufficient dietary intake, impaired absorption, or chronic blood loss (absolute ID); and/or reduced circulating iron linked to chronic inflammation, particularly seen in CV diseases (functional ID).[13,14] This inflammation leads to an increased release of hepcidin, a liver-expressed type II acute-phase protein and a major player in iron homeostasis by inhibiting iron absorption in the intestines and iron release from macrophages in the liver and spleen.[15] This mechanism contributes to ID observed in CV diseases. In HF, additional factors such as reduced bowel iron absorption due to generalized edema may also contribute to ID.[16,17] Ferritin levels can be artificially elevated in patients with CHF due to chronic inflammation.[34] Therefore, hepcidin has been proposed as a more sensitive index to evaluate ID.[6,18,19]

When iron levels are too low to support adequate hemoglobin synthesis, it can lead to IDA, which impairs the blood's ability to carry oxygen efficiently either due to a reduced number of red blood cells or low hemoglobin levels. While anemia can have various causes, ID is the most prevalent.[7]

According to European data, the prevalence of ID (with or without anemia) is 35% to 55% in outpatients with HF and 72% to 83% in patients admitted for HF.[20] A recent study in Alberta[21] used population-level data that included adult patients with HF between 2012 and 2019, to examine the prevalence of ID and IDA among patients with AHF and CHF. Among 17,463 patients with AHF, 38.5% had their iron status evaluated within 30 days postindex episode, compared to 34.2% of 11,320 patients with CHF. Of those tested, 72.6% and 73.9% of patients with AHF and CHF, respectively, were found to have ID, and 51.4% and 49.0% had IDA, respectively.

In addition to standard pharmacotherapy for HFrEF, the Canadian Cardiovascular Society guidelines[4] recommend assessing and treating ID in these patients. This approach aims to enhance exercise tolerance, improve quality of life, and reduce hospitalizations due to HF, supported by strong recommendations and moderate-quality evidence.[4,22]

As with the use of other HF treatments, management of ID in HF is suboptimal. TSAT is an important marker in these patients, with a value of less than 20% indicative of low plasma iron availability to tissues in patients with both absolute and functional ID. Canadian Cardiovascular Society guidelines[4] recommend consideration of IV iron therapy for patients with HF with all of the following: ejection fraction of 40% or less, and serum ferritin concentration of less than 100 mcg/L or between 100 mcg/L to 299 mcg/L in combination with a TSAT of less than 20%.[23,24]

Standards of Therapy

Contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following have been summarized and validated by the CDA-AMC review team.

The key goals in the treatment of ID and IDA are the correction of the hemoglobin deficit and repletion of iron stores (the correction phase), and maintenance of iron levels over time (the maintenance phase).[35,36]

Oral iron, often in the form of ferrous sulphate, is the first-line therapy for most cases of ID and IDA and is relatively safe, effective, and inexpensive. Some patients may be unable to absorb ferrous sulphate adequately due to impaired intestinal uptake resulting from GI disease or clinical conditions such as chronic inflammation, which may in turn lead to elevated levels of hepcidin.[37-39] In other instances, the rate of absorption of even high-dose oral ferrous sulphate is insufficient to correct the anemia and blood transfusion may be indicated.[37,40]

ID among patients with HF is known to be particularly recalcitrant to oral iron therapy, necessitating IV iron supplementation.[4,41] Because ID is an independent predictor of reduced functional capacity, increased hospitalization, and increased mortality for patients with HF, guidelines from the Canadian Cardiovascular Society, the Heart Failure Society of America, and the European Society of Cardiology all recommend starting patients who have ID with IV iron in preference to oral formulations, regardless of whether anemia is present.[4,26,27,41,42] The recently updated European Society of Cardiology guideline for the diagnosis and treatment of CHF and AHF recommends FCM or ferric derisomaltose as a treatment for symptomatic patients with HF with ID.[27] Similarly, recent guidelines from the American College of Cardiology recommend that in patients with HFrEF and ID with or without anemia, IV iron replacement is reasonable to improve functional status and quality of life.[25] Oral iron supplements are associated with GI side effects, which can have a detrimental impact on patient adherence to treatment.[35,36] A systematic review and meta-analysis of RCTs found an increased risk of GI side effects (OR = 2.32; 95% CI, 1.74 to 3.08; P < 0.0001), particularly constipation, nausea, and diarrhea.[43]

There is also a need to deliver iron rapidly in certain clinical situations including, for example, when a patient with ID requires an urgent surgery with risk of blood loss.[44] While repletion of iron stores with oral iron may require administration over several months, the correction of iron stores following IV iron administration occurs within a few weeks.[36,40] IV iron supplementation can, therefore, be an important treatment option in patients unable to absorb sufficient iron via the GI tract, unable to tolerate the required amounts of ferrous sulphate, and/or who require a rapid replenishment of stores. The IV route of iron administration can also benefit patients with poor adherence to other forms of treatment, chronic iron losses exceeding the rate of replacement possible with oral supplementation, and/or taking erythropoiesis-stimulating agent (ESA) treatment leading to increased demands. In patients taking ESAs, IV iron might significantly reduce ESA requirements and treatment costs.[40]

The earliest IV iron preparations were associated with acute toxicity resulting from the release of bioactive labile iron. Subsequent iron formulations (referred to as “second generation”) were complexes with nondextran carbohydrates, which release iron more slowly, such as iron sucrose and iron gluconate. Third-generation IV iron products, such as FCM and ferric derisomaltose, are formulated to be given in larger doses over a shorter period.[40]

In addition to FCM, there are currently 4 other IV iron products approved in Canada, albeit none are indicated specifically for patients with HF: Ferrlecit (sodium ferric gluconate complex in sucrose, 12.5 mg/

mL), Monoferric (ferric derisomaltose, 100 mg/mL), Venofer (iron sucrose, 20 mg/mL), and pms-Iron Sucrose (iron sucrose injection, 20 mg/mL). Of these products, none are indicated for use in pediatric populations.

Drug Under Review

FCM is a colloidal dispersion which contains iron in a stable ferric state.[24] This complex consists of a polynuclear iron-hydroxide core bound to a carbohydrate ligand. It is specifically formulated to provide easily utilizable iron for the body's iron transport and storage proteins, namely transferrin and ferritin.[24]

FCM was approved by Health Canada with the following indications:[24]

- the treatment of IDA in adult and pediatric patients aged 1 year and older when oral iron preparations are not tolerated or are ineffective
- the treatment of ID in adult patients with HF and NYHA class II or class III to improve exercise capacity.

The diagnosis of ID must be based on laboratory tests. The sponsor request for reimbursement is as per Health Canada indication for HF. A Notice of Compliance was issued on March 11, 2024.

The dosage of FCM is expressed as mg of elemental iron, with each mL containing 50 mg of elemental iron. The recommended dosing of FCM for adult patients follows a stepwise approach by first determining the individual iron need for repletion based on the patient's body weight and hemoglobin level (Table 4).

Table 4: Determination of the Total Iron Need in Adults (Aged ≥ 18 Years)

Hemoglobin		Patient body weight		
g/L	mmol/L	< 35 kg	35 kg to < 70 kg	≥ 70 kg
< 100	< 6.2	500 mg	1,500 mg	2,000 mg
100 to < 140	6.2 to < 8.7	500 mg	1,000 mg	1,500 mg
≥ 140	≥ 8.7	500 mg	500 mg	500 mg

Source: Product monograph for Ferinject.[24]

The maximum recommended cumulative dose of FCM is 1,000 mg of iron (20 mL FCM) per week. If the total iron need is higher, then the administration of an additional dose should be a minimum of 7 days apart from the first dose. A single FCM administration should not exceed either 15 mg iron/kg body weight, or 1,000 mg iron (20 mL FCM). Reassessment should be performed by the clinician based on the individual patient's condition. The hemoglobin level should be reassessed no earlier than 4 weeks after final FCM administration to allow adequate time for erythropoiesis and iron utilization. In the event the patient requires further iron repletion, the iron need should be recalculated.

Key characteristics of FCM are summarized in Table 5 with off-label IV treatments for ID in patients with HF. Sodium ferric gluconate (Ferrlecit), an IV iron formulation approved in Canada, is not represented here because of clinical expert input that this is not a comparator of interest in this population and may only be used in very uncommon, niche clinical circumstances among patients with kidney failure requiring other specific interventions.

Table 5: Key Characteristics of FCM, FD, and IS

Characteristic	FCM	FD	IS
Mechanism of action	FCM is a colloidal iron (III) hydroxide in complex with carboxymaltose.	FD is a colloid with strongly bound iron in spheroidal iron-carbohydrate particles. The FD formulation contains iron in a strongly bound complex that enables a controlled and slow release of bioavailable iron to iron binding proteins with little risk of free iron.	IS is dissociated by the reticuloendothelial system into iron and sucrose. The released iron replenishes body iron stores.
Indication[a]	For the treatment of ID in adult patients with heart failure and NYHA class II or class III to improve exercise capacity. The diagnosis of ID must be based on laboratory tests.	Treatment of ID anemia in adult patients who have intolerance or unresponsiveness to oral iron therapy. The diagnosis must be based on laboratory tests.	Treatment of ID anemia in the following patients: • Patients with NDD-CKD receiving an erythropoietin • Patients with NDD-CKD not receiving an erythropoietin • Patients with HDD-CKD receiving an erythropoietin • Patients with PDD-CKD receiving an erythropoietin
Route of administration	IV	IV	IV
Recommended dose	A single FCM administration should not exceed either: • 15 mg iron/kg body weight, or • 1,000 mg of iron (20 mL FCM). The maximum recommended cumulative dose of FCM is 1,000 mg of iron (20 mL FCM) per week. If the total iron need is higher, then the administration of an additional dose should be a minimum of 7 days apart from the first dose.	IV administration as drip infusion, bolus injection, or injection into venous limb of dialyzer. Total dosage based on iron need determined either from simplified table or Ganzoni formula. A single infusion should not exceed 20 mg iron/kg body weight or 1,500 mg.	Administration intravenously by slow injection or infusion. Administered as a total cumulative dose of 1,000 mg over a 14-day period as a 200 mg slow IV injection undiluted over 2 minutes to 5 minutes on 5 different occasions within the 14 day period.
Serious adverse effects or safety issues	Injectable iron products including FCM can cause serious allergic reactions, including fatal anaphylaxis or anaphylactoid reactions. FCM should only be given if personnel are able to treat severe allergic reactions without delay. Signs and symptoms of an allergic reaction should be monitored during each injection and for at least 30 minutes after your treatment with FCM.	Serious hypersensitivity reactions including life-threatening and fatal anaphylaxis/anaphylactoid reactions have been reported in patients receiving IV iron products including FD. Serious cases of hypotension. FD should only be administered when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. Patients should be carefully monitored for signs and symptoms of hypersensitivity reactions	Serious hypersensitivity reactions including life-threatening and fatal anaphylactic/anaphylactoid reactions have been reported in patients receiving IV iron products including iron sucrose injection. IS should only be administered when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.

Characteristic	FCM	FD	IS
		including monitoring of blood pressure and pulse during and for at least 30 minutes following each administration of FD.	

FCM = ferric carboxymaltose; FD = ferric derisomaltose; HDD-CKD = hemodialysis-dependent chronic kidney disease; ID = iron deficiency; IS = iron sucrose; NDD-CKD = non–dialysis-dependent chronic kidney disease; NYHA = New York Heart Association; PDD-CKD = peritoneal dialysis–dependent chronic kidney disease.

[a]Health Canada–approved indication.

Sources: Product monographs for ferric carboxymaltose,[24] ferric derisomaltose,[45] and iron sucrose.[46]

Perspectives of Patients, Clinicians, and Drug Programs

The full patient and clinician group submissions received by CDA-AMC are available in the consolidated patient and clinician group input document for this review on the project website.

Patient Group Input

This section was prepared by the CDA-AMC review team based on the input provided by patient groups.

No patient group input was submitted.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

All CDA-AMC review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of ID in patients with HF.

Unmet Needs

Although widely available and inexpensive, treatment of ID with oral iron was described by the expert to be of limited utility due to poor absorption in general, but especially among patients with HF due to a variety of physiological factors specific to HF, such as epithelial dysfunction in the gut because of mucosal edema and reduced intestinal blood flow. Oral iron is also associated with GI side effects that, as described by the clinical expert, can often lead to poor adherence. Oral iron is also limited in the dosage that can be consumed, which, compounded with the low rate of absorption, can result in very slow repletion. The expert also noted that oral administration of iron supplementation can interfere with the administration of other therapies, which can cause issues in a patient with HF who requires a concurrent cocktail of other medications to manage their underlying HF and improve their HRQoL.

The clinical expert indicated that IV iron is currently the preferred route for treatment of ID in patients with HF, and the intention of iron supplementation for ID in patients with HF is to improve HRQoL, functional capacity,

and exercise capacity. According to the clinical expert, iron repletion is not in itself necessarily expected or intended to directly or immediately impact outcomes such as mortality because iron replenishment is not directly affecting the disease process causing the HF. Rather, the effects of ID are the worsening of HRQoL, functional capacity, and exercise capacity, which IV iron treatment has shown clearly to benefit. These are also symptoms of HF and thus are particularly severe in patients with both ID and HF. Consequently, according to the clinical expert, treatment of ID associated with HF would be expected to provide particular benefit with regards to these effects.

Place in Therapy

European,[26,27] Canadian,[4] and American guidelines[25] for the management of ID in the setting of HF all recommend against oral iron and state preference for IV iron for repletion. The clinical expert described that IV iron preparations typically used in clinical practice include iron sucrose (maximum dose of 200 mg per sitting), ferric derisomaltose (maximum dose of 1,000 mg per injection), or FCM (maximum dose of 1,000 mg per week). Iron sucrose is a second-generation IV iron formulation, in contrast to ferric derisomaltose and FCM which are third generation, and according to the clinical expert are more thermodynamically stable and are designed to permit higher doses to be administered than previous generations. According to the clinical expert, first-generation IV iron formulations such as iron dextran are not used due to higher risks of anaphylaxis. Of the IV iron formulations, only FCM has a Health Canada–approved indication specific to the HF subpopulation; however, the other second-generation or third-generation IV iron preparations may also be used in clinical practice in this population.

Patient Population

The clinical expert described that ID is highly prevalent in patients with HF and is an independent predictor of worse functional capacity and outcome. Risk factors for ID according to the clinical expert include female sex, advanced HF, higher levels of N-terminal pro-brain natriuretic peptide and C-reactive protein. The expert noted that guidelines for the treatment of HF recommend all patients with HF should be tested for ID using serum ferritin and TSAT, and treatment with IV iron over oral iron is recommended for patients with ID and HF who meet other qualifying features that vary by regional guideline.

The expert highlighted that Canadian guidelines recommend consideration of IV iron therapy for patients with HF with all of the following: LVEF of 40% or less, and serum ferritin less than 100 mcg/L or between 100 mcg/L to 299 mcg/L with a TSAT less than 20%.

The clinical expert noted that there has been no assessment for the role of IV iron for anemia in patients with HF with preserved ejection fraction (HFpEF), a subgroup with poor prognosis and few condition-specific treatments impacting on survival. This is in contrast to patients HFrEF, for whom the Canadian guidelines do recommend IV iron supplementation if presenting with ID.

The clinical expert highlighted that the treatment guidelines do not delineate between NYHA classes with regards to treatment and rather determine who should receive which treatment based on clinical and objective factors such as ejection fraction, serum ferritin, and TSAT. Therefore, based on Canadian and

multiple international treatment guidelines for patients with HF and ID, patients with any NYHA class may potentially be suitable for treatment with IV iron formulations, including FCM.

Assessing the Response Treatment

The clinical expert consulted by CDA-AMC noted that assessing response should follow the treatment guidelines and product monographs, which lay out objective metrics for determining a patient's iron need and suitability for IV iron based on metrics such as ejection fraction (related to the patient's HF), serum ferritin, and TSAT. The clinical expert noted that, adverse reactions to treatment aside, there might be circumstances in which a patient could stop therapy, but this would depend on the etiology of their ID and therefore this should be identified in the event that it could be otherwise managed (e.g., GI-related blood loss). However, the clinical expert suggested that many patients would be expected to continue IV iron life-long given that HF is a chronic disease and any HF-related ID is unlikely to resolve spontaneously. The clinical expert did not feel that there was any evidence to suggest a generalized reason (e.g., a threshold of inadequate response) to stop therapy prematurely. Evidence of persisting ID requiring IV iron treatment per guidelines should, in their opinion, be the only determinant for coverage. Put differently, the only reason to discontinue treatment would be evidence that iron stores became consistently repleted such that guidelines no longer supported ongoing IV iron administration.

Discontinuing Treatment

The clinical expert stated that the majority of patients receiving IV iron supplementation would be expected to continue this therapy for the duration of their lives. Aside from intolerance or contraindication, there are no specific reasons to necessarily discontinue treatment with FCM in this population. The clinical expert highlighted that in patients with HF and ID, the ID is generally not expected to spontaneously resolve. The clinical expert also noted there is no circumstance in which a patient with HF and ID would be recommended to switch to oral iron supplementation rather than IV iron, although switching to a different IV formulation may be done based on physician discretion and patient preference.

Prescribing Considerations

IV iron formulations such as FCM are prescribed in hospital and can be ordered by any prescribing clinician managing the patient's HF and ID in that setting.

Clinician Group Input

This section was prepared by the CDA-AMC review team based on the input provided by clinician groups.

A diverse group of clinical experts responding to CDA-AMC call for input from clinician groups comprised 13 independent clinicians spanning multiple specialties. They gathered information from product monographs, published literature, and their extensive personal experiences.

According to the group, ID is a progressive condition that can lead to IDA if untreated, affecting various patient populations, including those with HF. For patients with comorbidities like HF, ID exacerbates symptoms, accelerates disease progression, and worsens prognosis. ID correlates with poorer functional capacity, increased hospitalizations, and increased mortality.

The clinician group emphasized that treatment goals include correcting hemoglobin deficits, replenishing iron stores, and maintaining them over time to alleviate symptoms and enhance HRQoL. While initial therapy often involves oral iron supplements, IV iron is recommended as the first-line treatment for patients with HF due to its rapid efficacy in iron repletion and its ability to improve outcomes. Guidelines advocate for initiating IV iron therapy as soon as ID is identified, regardless of anemia status. This strategy is especially beneficial for patients who cannot adequately absorb oral iron, experience intolerable GI side effects, or require higher rates of iron replacement, such as those receiving ESAs.

The clinician group noted that while IV iron formulations in Canada offer flexible dosing options to meet individual patient needs effectively, previous IV iron products posed significant challenges. These included requiring long administration periods or multiple sessions to achieve a cumulative dose of 1,000 mg. Additionally, none were indicated for use in pediatric populations or for the treatment of patients with ID and HF. This underscores the necessity for more efficient and versatile IV iron therapies capable of effectively addressing these treatment gaps. Newer IV iron products in Canada, like FCM, can deliver high doses (up to 1,000 mg) in a single injection or short infusion, which may reduce treatment burden, enhance convenience, and improve adherence, leading to faster symptom relief and better outcomes.

According to the clinician group, patients with HF and ID are particularly suitable for treatment with FCM. The clinician group indicated that treatment response is assessed using hematologic measures and iron parameters (ferritin and TSAT) to gauge improvements. Ideally, clinicians aim for normalization of hemoglobin levels and increased ferritin levels exceeding those indicating ID. Response evaluation should consider individual variations and potential challenges like ongoing blood loss or underlying health conditions. Clinically meaningful outcomes also include reducing the need for blood transfusions, symptom alleviation, enhanced exercise capacity, improved quality of life, and fewer hospitalizations. Monitoring typically occurs 4 weeks to 8 weeks after completing the initial treatment course to track progress and adjust therapy as needed.

According to the input, factors to consider when deciding to discontinue treatment with FCM include postrepletion assessments of hemoglobin, ferritin, and TSAT levels. Reassessment should occur no earlier than 4 weeks after the final dose to allow for adequate time for erythropoiesis and iron utilization. Treatment should be immediately discontinued in cases of hypersensitivity reactions or intolerance during administration, and it is contraindicated in patients with iron overload or persistent hypophosphatemia, where re-evaluation of treatment is warranted. FCM is appropriate for treatment in settings equipped to manage anaphylaxis and hypersensitivity reactions. It can also be administered in emergency departments or surgical inpatient units when indicated. While specialists like hematologists and other physicians commonly prescribe FCM, a specialist is not always required for diagnosis, treatment, and monitoring. Family medicine practitioners, as well as specialists in cardiology, gastroenterology, internal medicine, nephrology, and obstetrics and gynecology, among others, may also manage patients requiring IV iron therapy.

Drug Program Input

The drug programs provide input on each drug being reviewed through the CDA-AMC Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation. The

implementation questions and corresponding responses from the clinical experts consulted by CDA-AMC are summarized in Table 6.

Table 6: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
Relevant comparators may include ferric derisomaltose (Monoferric), iron sucrose (Venofer, generics), and sodium ferric gluconate complex (Ferrlecit) — although they do not have a specific Health Canada–approved indication for ID in patients with HF. Are these all considered relevant comparators? The comparator in the submitted trials was placebo or standard of care. Would a direct comparison against an off-label IV iron have been more appropriate or informative?	The clinical expert indicated that to their knowledge, iron sucrose and ferric derisomaltose are relevant comparators, but sodium ferric gluconate complex (Ferrlecit) is not used in Canada in this population. Notably, in the other indication (IDA in pediatric and adult patients in whom oral iron was inadequate, intolerable, or contraindicated), the clinical expert consulted for that indication noted that sodium ferric gluconate complex is rarely used and is intended for a very uncommon, niche population of patients. As such, it was not considered a relevant comparator for this review. The clinical expert agreed that a comparison to another IV iron, especially second-generation or third-generation formulations, would have been more appropriate and more informative than a comparison to placebo. The clinical expert noted that it is known that oral iron is less effective, especially in this population due to physiological impacts of HF that worsen the potential for iron uptake for oral formulations, and moreover, oral iron is not recommended in the HF treatment guidelines in Canada or internationally. In conclusion, the most reasonable comparator would be another IV iron formulation.
Considerations for initiation of therapy	
The product monograph indicates that patients must have a confirmed diagnosis of ID based on appropriate lab tests. The ferritin levels used in the inclusion criteria of the trials are consistent, but hemoglobin levels vary. How should ID be defined? Are there specific lab parameter thresholds related to ID that should be considered as initiation criteria in patients with HF?	The clinical expert expressed that the definition of ID should be based on Canadian treatment guidelines, and noted that hemoglobin levels can be low or changed for reasons other than ID, and this too blunt an instrument to diagnose ID. The 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure[4] states that the most widely accepted definition of ID in this population is a serum ferritin < 100 mcg/L or ferritin between 100 mcg/L and 299 mcg/L and transferrin saturation < 20%. However, the guidelines also state that ID can be difficult to diagnose in patients with HF and diagnosis should ideally be done in a clinically stable state, and furthermore, new biomarkers (such as soluble transferrin receptor, hepcidin, and reticulocyte hemoglobin) might improve the sensitivity and specificity of ID diagnosis in the future, and their clinical utility has yet to be shown. Suggested commonly available tests for the work-up of ID and IDA in the guidelines also include investigations for several other suspected etiologies, including GI-related blood loss (fecal occult blood, upper and lower endoscopy), thyroid-related disorders (thyroid-stimulating hormone), nutritional deficiency (vitamin B12), thalassemia or sickle cell disease (hemoglobin electrophoresis), multiple myeloma, amyloidosis, other protein disorders (serum and urine protein electrophoresis). Additional tests performed to investigate multiple and other etiologies include peripheral smear, reticulocyte count/index, lactate dehydrogenase, haptoglobin, bone marrow biopsy.

Drug program implementation questions	Clinical expert response
Oral iron is the first-line therapy for most patients with ID and/or IDA (and is inexpensive). Should patients with ID and HF be required to trial at least 1 oral iron therapy or be intolerant or have a contraindication to oral iron therapy (similar to patients with IDA)? If so, what would be considered an appropriate trial in this patient population? How would intolerance or contraindication be defined?	The clinical expert stated that oral iron is not recommended in patients with HF and ID and has been demonstrated to be insufficiently effective in this patient population.[47] The expert explained that there are complex physiological reasons that a patient with HF typically has decreased uptake of oral iron than the general population as a result of their HF. Therefore, a patient with diagnosed HF and ID should not be required to trial any oral iron preparation nor should they need to be intolerant or have a contraindication to any oral iron therapy before receiving an IV iron formulation. The best clinical practice in HF and ID for iron repletion has been well-defined as IV iron formulations, exclusively, in the Canadian[4] and multiple international treatment guidelines.[25-27]
The AFFIRM-AHF trial for patients with AHF and ID did not meet its primary end point. Should patients with ACH be considered for coverage, or should coverage be limited to patients with CHF?	The clinical expert noted that between ACH or CHF, it is the patients with chronic disease who will generally have the greatest need for ongoing inpatient treatment and, in the context of ID, the greatest need for iron repletion. Depending on the etiology, a patient with AHF that resolves after treatment of the acute episode may not require ongoing treatment thereafter. However, the clinical expert explained that, in most cases, there is no reason to exclude patients with AHF and ID from iron repletion, and treatment guidelines do not distinguish between AHF and CHF in their recommendations for management of concurrent ID. Patients with AHF may progress to CHF and the distinction between these categories may be uncertain. Additionally, patients with ID or IDA may typically benefit in exercise capacity and health-related quality of life given appropriate iron supplementation, and in the setting of HF, the recommended manner of providing iron supplementation is by IV formulations.
Considerations for continuation or renewal of therapy	
The product monograph notes that reassessment of hemoglobin should be performed no earlier than 4 weeks after final Ferinject administration to allow adequate time for erythropoiesis and iron utilization. How would therapeutic response to supplemental iron be assessed in patients with ID and CHF? Is hemoglobin level alone sufficient?	The clinical expert highlighted that hemoglobin is a blunt instrument that, alone, should not be used to diagnose or evaluate ID. The clinical expert stated that reduced or changed hemoglobin level may have a wide variety of etiologies that may or may not be related to depleted iron stores and could co-occur with HF, with or without ID (e.g., chronic kidney disease, inflammation, hemodilution, rarer nutritional deficiencies [vitamin B12, folic acid, thiamine], GI blood loss, medication side effects, and so forth). Hemoglobin is a standard assessment in the work-up of anemia in general, as well as in the context of HF and ID, and additionally, lower hemoglobin levels are associated with worse outcomes in HF; however, hemoglobin alone provides an insufficient assessment of ID. Management of ID with parenteral iron requires monitoring of, among other things, hemoglobin and other iron parameters such as ferritin and transferrin saturation. The clinical expert underscored that the Canadian treatment guidelines suggest ferritin and transferrin saturation are measured as a common work-up for diagnosis of ID, but that new biomarkers continue to emerge as potential contenders for more sensitive and specific ID diagnosis. The clinical expert also noted that many patients with HF and ID are expected to require iron supplementation for the duration of their lifetime. As such, there was no threshold of any laboratory parameter under which the drug should be discontinued due to lack of efficacy.

Drug program implementation questions	Clinical expert response
	The expert stated that treatment should be required for as long as dictated by guideline criteria for ID-related IV iron replacement therapy.
Considerations for discontinuation of therapy	
Under what circumstances should ferric carboxymaltose (Ferinject) be discontinued in a patient with HF and ID?	So long as guideline criteria for iron replacement therapy remain the same, and aside from intolerable AE or patient or clinician decision or preference, there are no specific reasons to require discontinuation of ferric carboxymaltose in a patient with HF and ID.
Considerations for prescribing of therapy	
Doses can range from 500 mg to 2,000 mg, depending on hemoglobin level and body weight. The maximum recommended dose of ferric carboxymaltose is 1,000 mg of iron per week; thus patients requiring higher doses will require a second dose administered a minimum of 7 days from the first dose. How often do patients with ID and HF require doses of iron greater than 1,000 mg?	The clinical expert was uncertain and expected it is uncommon.
Currently, coverage for IV iron by public drug programs is not restricted by specialist type.	This is a comment from the drug programs to inform CDEC deliberations.
Care provision issues	
Ferric carboxymaltose (Ferinject) is administered intravenously. Patients need to be monitored for hypersensitivity reactions during and for at least 30 minutes after administration.	This is a comment from the drug programs to inform CDEC deliberations.
System and economic issues	
Due to the need for access to IV infusion centres for administration of IV iron, funding for outpatients may vary between jurisdictions, or funding may be through special programs or provided through health authorities.	This is a comment from the drug programs to inform CDEC deliberations.

AE = adverse event; AHF = acute heart failure; CDEC = Canadian Drug Expert Committee; CHF = chronic heart failure; GI = gastrointestinal; HF = heart failure; ID = iron deficiency; IDA = iron deficiency anemia.

Clinical Evidence

The objective of this CDA-AMC Clinical Review Report is to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of Ferinject (ferric carboxymaltose) for the treatment of ID in adult patients with HF and NYHA class II or class III to improve exercise capacity. The focus will be placed on comparing FCM to relevant comparators and identifying gaps in the current evidence.

A summary of the clinical evidence included by the sponsor in the review of FCM is presented in 4 sections with the CDA-AMC critical appraisal of the evidence included at the end of each section. The first section, the systematic review, includes pivotal studies and RCTs that were selected according to the sponsor's systematic review protocol. The CDA-AMC assessment of the certainty of the evidence uses the GRADE

approach and follows the critical appraisal of the evidence. Subsequent sections would detail long-term extension studies, indirect evidence, and studies addressing gaps in the evidence, but there were no studies of interest submitted for this indication.

Included Studies

Clinical evidence from the following are included in the CDA-AMC review and appraised in this document:

- 4 pivotal studies or RCTs identified in systematic review.

Systematic Review

Contents within this section have been informed by materials submitted by the sponsor. The following have been summarized and validated by the CDA-AMC review team.

Description of Studies

Characteristics of the included studies are summarized in Table 7. Ideally, studies of interest would compare FCM to other IV infusion formulations of iron supplementation; however, no such studies exist to our knowledge. The studies included were the FAIR-HF study (N = 459), CONFIRM-HF study (N = 304), and HEART-FID (N = 3,065) study in patients with CHF, and the AFFIRM-AHF study (N = 1,132) in patients with AHF, all 4 of which are placebo-controlled, double-blind, randomized phase III (FAIR-HF and HEART-FID) or phase IV (CONFIRM-HF and AFFIRM-AHF) trials in adults with HF and ID. Of these, 2 studies (FAIR-HF and CONFIRM-HF) were focused primarily on clinical efficacy outcomes such as exercise capacity and NYHA class, while the remaining 2 studies (HEART-FID and AFFIRM-AHF) were focused primarily on composite outcomes related to hospitalizations and deaths (the HEART-FID study also included the 6MWT in their composite primary outcome). The studies ranged in duration from approximately 6 months (the FAIR-HF study) to 12 months (the CONFIRM-HF, HEART-FID, and AFFIRM-AHF studies).

Some studies of adults with HF and ID were excluded from consideration in this review. Studies that compared to oral iron were not considered to be of interest because oral iron has been demonstrated to be ineffective in iron repletion in this population, is not recommended in this population by Canadian[4] and international[25-27] treatment guidelines for the management of HF, and was confirmed by the clinical expert consulted by CDA-AMC to be an inappropriate choice of treatment among patients with HF because of physiological consequences of HF that lower the ability of the body to absorb iron administered orally. One study that was potentially of interest, the EFFECT-HF study (N = 174), was excluded because the comparator arm was standard of care and 29 of 86 patients in the standard of care treatment group were receiving oral iron.

Other studies with similar populations were excluded due to small sample sizes and because it was not believed they would contribute to the overall conclusions of this review to an important degree (the Caravita et al.,[70] Martens et al.,[71] Nunez et al.,[72] and FER-CARS-01 studies[73]). The characteristics of these studies, in addition to the EFFECT-HF study, are summarized briefly in Appendix 1.

Table 7: Details of Studies Included in the Systematic Review

Detail	FAIR-HF	CONFIRM-HF	HEART-FID	AFFIRM-AHF
Designs and populations				
Study design	Multicentre Double blind Parallel Randomized 2:1 Placebo controlled Phase III	Multicentre Double blind Parallel Randomized 1:1 Placebo controlled Phase IV	Multicentre Double blind Parallel Randomized 1:1 Placebo controlled Phase III	Multicentre Double blind Parallel Randomized 1:1 Placebo controlled Phase IV
Locations	75 sites in Europe and Argentina	41 sites screened patients and 39 randomized patients in 9 countries in Europe	344 sites in North America, Europe, and New Zealand, and Australia	121 sites in Europe, South America, and Singapore
Patient enrolment dates				
Randomized (N)	**Total:** 459 **Intervention:** 304 **Comparator:** 155	**Total:** 304 **Intervention:** 152 **Comparator:** 152	**Total:** 3,065 **Intervention:** 1,532 **Comparator:** 1,533	**Total:** 1,132 **Intervention:** 567 **Comparator:** 565
Inclusion criteria	• Aged ≥ 18 years • NYHA functional class II or class III due to stable symptomatic CHF • 2 weeks without cardiac hospitalization • Patients in NYHA class II must have had an unplanned hospital admission or emergency department visit for worsening of HF within 12 months before randomization • On optimal conventional therapy[a] • No dose changes of HF drugs in last 2 weeks with the exception of diuretics, nor new HF drugs during last 4 weeks • LVEF ≤ 40% (NYHA class II) or LVEF	• Aged ≥ 18 years • Stable CHF (NYHA class II or class III functional class) • On optimal background therapy[a] for at least 4 weeks with no dose changes of HF drugs during last 2 weeks (with exception for diuretics) • LVEF ≤ 45% at screening • BNP > 100 pg/mL and/or N-terminal-pro-BNP > 400 pg/mL at screening • Serum ferritin < 100 mcg/mL or 100 mcg/mL to 300 mcg/mL with TSAT < 20%	• Aged ≥ 18 years • Stable HF (NYHA class II to class IV) on maximally tolerated background therapy[a] for at least 2 weeks before randomization • LVEF ≤ 40% at screening, or either historical value of ejection fraction ≤ 40% within 24 months of screening visit or historical value of ejection fraction ≤ 30% within 36 months of screening visit • Hemoglobin > 9.0 g/dL and < 13.5 g/dL (females) or < 15.0 g/dL (males) within 28 days of randomization • Serum ferritin < 100 mcg/mL or 100 mcg/mL to 300 mcg/mL with TSAT < 20%	• Aged ≥ 18 years • Hospitalized for AHF • Upon admission for the AHF episode, persistent dyspnea at rest in a recumbent sitting position (30° to 45°) or with minimal exertion • Concomitant iron deficiency (ferritin < 100 mcg/L, or 100 to 299 mcg/L with TSAT < 20%) • During the index hospitalization, patients had to have received at least 40 mg of IV furosemide (or equivalent) and had LVEF < 50% within 12 months before randomization

Detail	FAIR-HF	CONFIRM-HF	HEART-FID	AFFIRM-AHF
	≤ 45% (NYHA class III) • Hemoglobin ≥ 9.5 g/dL and ≤ 13.5 g/dL • Ferritin < 100 mcg/L, or < 300 mcg/L when TSAT is < 20%		• Documented hospitalization for HF within 12 months of enrolment or elevated N-terminal-pro-BNP within 90 days of randomization	
Exclusion criteria	• History of acquired iron overload • Known active infection • Chronic liver disease and/or screening ALT or AST > 3 times the upper limit of normal • Anemia due to reasons other than iron deficiency (e.g., hemoglobinopathy) • Immunosuppressive therapy or renal dialysis, currently or planned within the next 6 months • History of erythropoietin, IV or oral iron therapy, and blood transfusion in previous 12 weeks and/or such therapy planned within the next 6 months (lack suitability) for the FAIR-HF study, and history of erythropoietin-stimulating agent use, IV iron therapy, and/or blood transfusion in previous 6 weeks before randomization for the CONFIRM-HF study • Unstable angina pectoris, uncorrected valvular disease or LV outflow obstruction, obstructive cardiomyopathy, poorly controlled fast atrial fibrillation or flutter, or poorly controlled symptomatic bradyarrhythmias or tachyarrhythmias • Acute MI, acute coronary syndrome, TIA, or stroke within last 3 months • Coronary artery bypass graft, percutaneous intervention (cardiac, cerebrovascular, aortic), or major surgery, including thoracic and cardiac surgery, within the last 3 months • Vitamin B12 or folate deficiency		• History of acquired iron overload • Recent (within 3 months) receipt of erythropoietin-stimulating agent, IV iron therapy, or blood transfusion • Acute MI, acute coronary syndrome, TIA, or stroke within 30 days of enrolment	• Dyspnea due to noncardiac causes • Signs of active infection • Documented restricted amyloid myocardiopathy, acute myocarditis, or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy • Clinical evidence of acute coronary syndrome, TIA, or stroke within last 30 days • Severe valvular or LV outflow obstruction needing intervention • Major cardiac surgery within last 3 months • Body weight < 35 kg • Anemia not attributable to iron deficiency • History of erythropoietin-stimulating agent, IV iron therapy, and/or blood transfusion in prior 3 months • Renal dialysis • Receiving system chemotherapy and/or radiotherapy or has a known active malignancy of any organ system • Chronic liver disease and/or screening ALT or AST > 3 times the upper limit of normal

Detail	FAIR-HF	CONFIRM-HF	HEART-FID	AFFIRM-AHF
Drugs				
Intervention	FCM solution containing 5% w/v iron Administered in doses of 200 mg iron (4 mL) weekly up to iron repletion (variable duration depending on individual iron deficit [b] rounded to nearest 100); the final dose may have been only 100 mg iron (2 mL) depending on individual iron deficit[c] Maintenance phase: after correction, given monthly in doses of 200 mg (4 mL) until week 24	FCM solution containing 5% w/v iron; doses of 500 mg iron (10 mL) or 1,000 mg iron (20 mL); total repletion doses ranged from 500 mg to 2,000 mg iron, with the maximum individual dose being 1,000 mg iron Correction phase (based on weight and hemoglobin at screening) and maintenance dosing phase (based on serum ferritin and TSAT levels at weeks 12, 24, and 36) Undiluted bolus IV over approximately 1 minute Day 1 and week 6: 1,000 mg or 500 mg dose (depending on hemoglobin ≤ 14 g/dL or > 14 g/dL) Weeks 12, 24, and 36: maintenance doses of 500 mg if applicable (i.e., serum ferritin < 100 mcg/mL, or serum ferritin 100 mcg/mL to 300 mcg/mL and TSAT < 20%)	FCM supplied in 15 mL vials containing 750 mg as a continuous infusion or slow IV injection at a rate of 2 mL (100 mg) per minute (estimated approximately 7.5 minutes) for patients weighing > 50 kg For patients weighing < 50 kg, dose adjusted to 15 mg/kg 30-minute postadministration observation	FCM administered as undiluted bolus Supplied in 10 mL vials containing 500 mg iron The dose of study treatment to be administered was to be determined using the patient's body weight and hemoglobin values based on a repletion and maintenance dosing scheme Visit 2 and visit 3 (week 0 and week 6, repletion phase): initial dose of 10 mL or 20 mL depending on weight and hemoglobin Visit 4 and visit 5 (week 12 and week 24, maintenance phase): dose of 10 mL only if deficiency persists
Comparator(s)	Normal saline (0.9% w/v as sterile solution in water) in doses of 2 mL or 4 mL	Normal saline (0.9% w/v as sterile solution in water)	Normal saline (0.9% w/v as sterile solution in water) supplied as 15 mL fill in 20 mL vials	Normal saline (0.9% w/v as sterile solution in water)
Study duration				
Screening phase	Up to 2 weeks before first dose of study medication	Up to 4 weeks	Up to 28 days	NR
Treatment phase	**Iron repletion correction phase:** Up to 9 weeks; variable number of dosing visits depending on individual iron deficit,[b] minimum of 3 to maximum of 9 **Iron maintenance phase:** First dose in maintenance phase scheduled 3 weeks to 6	**Iron repletion correction phase**: At baseline and week 6 **Iron maintenance phase:** At week 12, 24, and 36	Dosing at day 0 and day 7, and then every 6 months as applicable up to 12 months	Up to week 24

Detail	FAIR-HF	CONFIRM-HF	HEART-FID	AFFIRM-AHF
	weeks after last visit of correction phase **The total treatment period** (correction plus maintenance phase) should be 24 (± 2) weeks			
Follow-up phase	Follow-up visit 2 weeks (± 3 days) after last study drug administration	Up to week 52	In line with treatment phase	Up to week 52
Outcomes				
Primary end point	• Self-reported PGA at week 24 • Change in NYHA class from baseline to week 24	Change in 6MWT from baseline to week 24	Hierarchical composite including death (at 12 months), hospitalization for HF (at 12 months), and change in 6MWT (baseline to 6 months) distance	The composite of recurrent HF hospitalizations and CV death up to 52 weeks after randomization
Secondary and exploratory end points	**Secondary efficacy:** • PGA at week 4 and week 12 • Change in NYHA class from baseline to week 4 and week 12 • Change in 6MWT from baseline to week 4, week 12, and week 24 **HRQoL:** • Change in KCCQ (overall summary score and symptom frequency score) and EQ-5D (total score) from baseline to week 4, 12, and 24 **Safety:** • Days alive and out of hospital • Hospitalization rate (total, due to CHF, or other CV causes) • Time to first hospitalization for worsening of CHF • Change in eGFR • AEs and mortality • Vital signs and clinical laboratory panels	**Secondary:** • PGA score at weeks 6, 12, 24, 36, and 52 • Change in NYHA class at weeks 6, 12, 24, 36, and 52 • Change in 6MWT distance from baseline to weeks 6, 12, 36, and 52 • Change in fatigue score from baseline to weeks 6, 12, 24, 36, and 52 • Change in KCCQ from baseline to weeks 6, 12, 24, 36, and 52 (overall summary score and symptom frequency score) • Change in EQ-5D total score from baseline to weeks 6, 12, 24, 36, and 52 • Cumulative iron requirements and number of iron administrations over the study period **Safety and related efficacy end points:**	**Secondary:** • Time to CV death or hospitalization for HF • Time to CV death or CV hospitalization • Time to CV death • Time to CV death or intervention for worsening HF ◦ Hospitalization for HF ◦ Urgent HF visits • Change in 6MWT at 12 months	**Secondary:** • The composite of recurrent CV hospitalizations and CV death up to 52 weeks after randomization • HF hospitalizations up to 52 weeks after randomization (analyzed as recurrent event) • CV mortality analyzed as time to first event at 52 weeks after randomization • The composite of HF hospitalizations or CV death analyzed as time to first event at 52 weeks after randomization • Days lost due to HF hospitalizations or CV death at 52 weeks after randomization **Other:** • Several additional composite outcomes and metrics of hospitalizations • AEs and mortality

Detail	FAIR-HF	CONFIRM-HF	HEART-FID	AFFIRM-AHF
	• 12-lead ECG **Health economics:** • Health resource utilization • Direct, indirect, and total costs from payer and societal perspectives • Cost-effectiveness	• Change from baseline to weeks 6, 12, 24, 36, and 52 in clinical laboratory panels and eGFR • AEs and mortality • Hospitalization rate (total, due to CHF, due to other CV causes) • Days alive and out of hospital • Time to death, first hospitalization for worsening HF		• Clinical laboratory panels and cardiac biomarkers
Publication status				
Publications	• Anker et al. (2009)[48] • Comin-Colet et al. (2013)[49] • NCT00520780 • EUCTR2006 to 004608 to 37-DE	• Ponikowski et al. (2015)[50] • NCT01453608 • EUCTR2011 to 001695 to 19-AT	• Mentz et al.[31] • NCT03037931	• Jankowska et al. (2021)[51] • Ponikowski et al. (2020)[52] • NCT02937454

6MWT = 6-minute walk test; AE = adverse event; AHF = acute heart failure; ALT = alanine transaminase; AST = aspartate transferase; BNP = brain natriuretic peptide; CHF = chronic heart failure; CV = cardiovascular; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FCM = ferric carboxymaltose; HF = heart failure; HRQoL = health-related quality of life; KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricle; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; NR = not reported; PGA = Physician's Global Assessment; TIA = transient ischemic attack; TSAT = transferrin saturation; w/v = weight per volume.

[a]In general, optimal pharmacological treatment which includes a diuretic, a beta-blocker, and/or an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker as determined by the investigator, unless contraindicated or not tolerated.

[b]Iron deficit (mg) = body weight (kg) × (150 – actual hemoglobin [g/L]) × 0.24 + 500 mg (depot iron). In patients with a body mass index > 25 kg/m^2, a normalized weight will be used to calculate the iron deficit. Body mass index is calculated as weight (kg)/(height [m] x height [m]) and normalized weight (kg) is calculated as 25 × height (m) × height (m). The factor of 0.24 in the calculation of iron deficit is calculated as: 0.0034 (as iron content of hemoglobin = 0.34%) × 0.07 (as blood volume = 7% of body weight) × 1,000 (conversion of g to mg).

[c]Ferinject was administered in doses of 200 mg (4 mL) weekly up to iron repletion (correction phase of variable duration depending on individual iron deficit). The calculated dose was rounded to the next 100 mg of iron, (i.e., the final dose may be 100 mg of iron depending on the individual iron deficit). After the correction phase, FCM was given monthly in doses of 200 mg until the 24th week (maintenance phase). Total dose required was calculated using the Ganzoni formula (and administered in first 12 weeks) with a maintenance dose administered from week 12 at 200 mg every 4 weeks until week 24. If ferritin was > 800 mcg/L or > 500 mcg/L when TSAT was > 50%, or hemoglobin was > 16.0 g/dL at any stage of treatment, iron treatment was discontinued and placebo was administered instead.

Sources: Clinical Study Reports, Statistical Analysis Plans, and Protocols for the FAIR-HF,[29] CONFIRM-HF,[30] and AFFIRM-AHF studies;[32] publication, supplementary appendix, and protocol of the HEART-FID study.[31]

Populations

Inclusion and Exclusion Criteria

All 4 studies included adult patients with NYHA class II or class III, although the HEART-FID study also included class IV, and the AFFIRM-AHF study also included both class I and class IV. The 3 CHF studies had a maximum allowed LVEF at screening or index visit, although the precise threshold varied: 40% or less (NYHA class II) or LVEF of 45% or less (NYHA class III) in the FAIR-HF study, 45% or less in the CONFIRM-HF study, and 40% or less in the HEART-FID study (although historically reduced LVEF was also allowed given specific circumstances). In the AFFIRM-AHF study, the inclusion criteria required that patients had

a LVEF of less than 50% within 12 months before randomization. All 4 included studies required a serum ferritin of less than 100 mcg/mL, or 100 mcg/mL to 299 mcg/mL or 100 mcg/mL to 300 mcg/mL with a TSAT of less than 20%. The exclusion criteria were relatively similar across trials with no notable concerns for interpretation of the evidence.

Interventions

All 4 studies compared FCM (5% weight by volume in water for injection) to placebo.

In the FAIR-HF study, the dosage form was 2 mL vials containing 100 mg of iron per vial, in a 5% weight by volume solution. Placebo was in the form of 5 mL containers of normal saline at a concentration of 0.9% weight by volume. Because these appear visually different, preparation and administration of the solutions for injection was completed by an unblinded study person using black syringes, with recommendations for steps to maintain blinding of the patient and outcome assessors. Dosing was divided between a “correction phase” and “maintenance phase.” Each injection of either FCM or placebo was given in a volume of 4 mL (corresponding to 200 mg iron in the FCM group), with the exception of the last injection of the correction phase, which could be 2 mL (100 mg iron in the FCM group). Total iron dosing for repletion was calculated using the Ganzoni formula. The correction phase included weekly doses of 200 mg iron (or corresponding volume of placebo [4 mL saline]) until iron repletion was achieved, rounded to the next 100 mg. After the correction phase, doses were given on a monthly basis in a volume of 4 mL (i.e., 200 mg iron in the FCM group) until week 24. In terms of concomitant medications, patients were not allowed to participate in the trial if they were on immunosuppressive therapy, had a previous heart transplant, or were on renal dialysis. Prescription or administration of erythropoietin, IV or oral iron therapy, and blood transfusion concomitantly with study treatment was not allowed, because these agents can induce an increase of iron blood parameters and overlap the effect of IV iron therapy, hence mislead the evaluation of efficacy and safety of IV iron therapy in patients with CHF.

In the CONFIRM-HF study, the dosage form was 10 mL vials containing 500 mg iron per vial. Placebo was in the form of a 5 mL, 0.9% weight by volume sodium chloride solution in water for injection. Because these appear visually different, preparation and administration of the solutions for injection was completed by an unblinded study person using black syringes, with recommendations for steps to maintain blinding of the patient and outcome assessors. Unlike the FAIR-HF study, the CONFIRM-HF study did not use the Ganzoni formula for calculating iron need; instead, the regimen was simplified based on screening weight and hemoglobin levels. Correction of ID was done with a cumulative dose of 500 mg to 2,000 mg of iron, with up to 3 additional maintenance doses of 500 mg thereafter. On day 0, patients receiving FCM received an initial single dose of 1,000 mg, or 500 mg for those with hemoglobin greater than 14 g/dL; patients allocated to placebo instead received 4 vials of saline to match the volume. At week 6, patients received an additional dose based on weight and hemoglobin: patients weighing less than 70 kg at screening and with hemoglobin of less than 10 g/dL at week 6 received 10 mL (500 mg) or 2 vials of saline; patients with a screening weight of 70 kg or greater received either 20 mL corresponding to 1,000 mg of FCM (or 4 vials saline) if their hemoglobin was less than 10 g/dL or 10 mL corresponding to 500 mg of FCM (or 2 vials saline) if their hemoglobin was between 10 g/dL to 14 g/dL. No dose was given to patients who either weighed less than 70

kg and had a hemoglobin reading of 10 g/dL to 14 g/dL, or weighed 70 kg or greater and had a hemoglobin greater than 14 g/dL. At weeks 12, 24, and 36, as maintenance dosing, patients could receive 10 mL (500 mg) of FCM (or 2 vials of saline) if their serum ferritin was still less than 100 mcg/mL or was between 100 mcg/mL to 300 mcg/mL and their TSAT was less than 20%. In terms of concomitant therapy, prohibited therapies during the study included other parenteral iron therapy, oral iron therapy (albeit ongoing use of multivitamins containing < 75 mg/day of iron was permitted), red cell transfusions, or ESAs.

In the HEART-FID study, FCM was available in 15 mL vials containing 750 mg and administered as either a continuous infusion or a slow IV injection at a rate of 2 mL (100 mg) per minute for a total dose of 750 mg per injection for patients weighing greater than 50 kg. For patients weighing less than 50 kg, the dose was adjusted to 15 mg/kg per injection. Patients received 2 doses separated by 7 (± 2) days. The Ganzoni formula was not used to calculate iron need, based on the justification that the US label (at the time approved for IDA) outlined dosing as previously described based on whether patients weigh at least 50 kg or not, and that the Ganzoni formula is theoretical and may not be applicable to all disease states or clinical scenarios (according to the study protocol publication). Placebo (normal saline) dosing volume was adjusted for weight to maintain blinding. Blinding of patients was maintained using blindfolds or curtains so that they could not see the vials being injected. Blinded study personnel were blinded to posttreatment iron indices and serum phosphorous laboratory results due to the potential for these to break the blind. Patients could receive additional doses of study drug every 6 months; patients in the FCM group were dosed based on hemoglobin levels (< 13.5 g/dL in females or < 15.0 g/dL in males) and iron studies (ferritin < than 100 mcg/mL, or between 100 mcg/mL to 300 mcg/mL with TSAT < 20%), while patients in the placebo group received matching volumes of placebo based on these parameters. Blinded staff administered assessments such as the 6MWT and other examinations. The HEART-FID study disallowed patients who had recently received (within 3 months) ESA, IV iron therapy, or blood transfusion; with current or planned mechanical circulatory support or heart transplant; and with hemodialysis or peritoneal dialysis currently or planned within 6 months.

In the AFFIRM-AHF study, the dosage form was the same as in the CONFIRM-HF study (i.e., 10 mL vials containing 500 mg iron per vial, a concentration of 5% weight by volume). Similar to both the FAIR-HF and CONFIRM-HF studies, due to this solution being dark brown and the saline (0.9% weight by volume, 10 mL vial) solution being clear, preparation was completed using black syringes with steps taken to maintain blinding of study patients and blinded personnel performing study assessments. Calculation of total iron need was done in a similar manner to the CONFIRM-HF study (i.e., a simplified algorithm not using the Ganzoni formula). Administration of study drug or placebo was done in 10 mL volumes (i.e., 500 mg iron in the FCM group) at each injection. At week 0, all patients received 10 mL of either FCM or placebo solution. At week 6, patients received an injection of 10 mL if they had either a hemoglobin level of less than 10 g/dL (received 10 mL if < 70 kg or 20 mL if ≥ 70 kg), or if they weighed 70 kg or greater and had a hemoglobin level of 10 g/dL to 14 g/dL, inclusive (received 10 mL). Patients outside of these parameters (i.e., higher hemoglobin level) did not receive a week 6 dose. At week 12 and week 24, patients could receive a 10 mL dose (i.e., 500 mg iron) if ID persisted, which was defined as serum ferritin of 100 mcg/mL, or serum ferritin of 100 mcg/mL to 299 mcg/mL inclusive if TSAT was less 20%. As an aside, in the Netherlands, Spain, and Singapore, patients with a hemoglobin level less than 10 g/dL were withdrawn from further study dosing due to differences in

the eligibility criteria in those countries. In terms of concomitant medications, the following therapies were disallowed, and if required then the patient was to withdraw from the study treatment: immunosuppressive or myelosuppressive therapy, erythropoietin, oral or IV iron therapy other than study medication (albeit ongoing use of multivitamins containing < 75 mg/day of iron was permitted), blood transfusion, surgery that could result in significant blood loss, renal dialysis, or heart transplant.

Outcomes

A list of efficacy end points assessed in this Clinical Review Report is provided in Table 8, followed by descriptions of the outcome measures. Summarized end points are based on outcomes included in the sponsor's Summary of Clinical Evidence as well as any outcomes identified as important to this review according to the clinical expert consulted by CDA-AMC and input from clinician groups and public drug plans. Patient group input would normally be considered but none was submitted. Using the same considerations, the review team selected end points that were considered to be most relevant to inform Canadian Drug Expert Committee deliberations and finalized this list of end points in consultation with members of the expert committee. All summarized efficacy end points were assessed using GRADE. Where outcomes of interest were reported as components of composite outcomes in some trials, these composites were descriptively summarized but not assessed using GRADE.

Table 8: Outcomes Summarized From the Studies Included in the Systematic Review

Outcome measure	Time point	FAIR-HF	CONFIRM-HF	HEART-FID	AFFIRM-AHF
NYHA class	Change from baseline to: • 24 weeks (or 6 months) • 52 weeks (or 12 months)	Primary (24 weeks) NR at 52 weeks	Secondary (24 and 52 weeks)[a]	NR	"Other" end point (24 and 52 weeks)[a]
6MWT	Change from baseline to: • 24 weeks (or 6 months) • 52 weeks (or 12 months)	Main secondary (24 weeks)[a] NR at 52 weeks	Primary (24 weeks)[a] Secondary (52 weeks)[a]	Assessed as the third and final submeasure in a hierarchical composite (wherein the composite outcome is the primary outcome), from baseline to 6 months[a] Secondary (12 months)[a]	NR
KCCQ	Change from baseline to: • 24 weeks (or 6 months) • 52 weeks (or 12 months)	Main secondary (24 weeks)[a] NR at 52 weeks	Secondary (24 and 52 weeks)[a]	NR	Secondary (24 and 52 weeks)[a]

Outcome measure	Time point	FAIR-HF	CONFIRM-HF	HEART-FID	AFFIRM-AHF
Fatigue score	Change from baseline to: • 24 weeks (or 6 months) • 52 weeks (or 12 months)	NR	Secondary (24 and 52 weeks)[a]	NR	NR
Serum ferritin (mcg/L)	Change from baseline to: • 24 weeks (or 6 months) • 52 weeks (or 12 months)	Laboratory evaluation (24 weeks)[a] NR at 52 weeks	Laboratory evaluation (24 and 52 weeks)[a]	Laboratory evaluation (24 and 52 weeks)[a]	Laboratory evaluation (24 and 52 weeks)[a]
Hospitalization rate due to any CV reason	Through: • 24 weeks (or 6 months) • 52 weeks (or 12 months)	Safety (24 weeks)[a] NR at 52 weeks	Safety (24 and 52 weeks)[a]: due to "worsening of CHF" and "for other CV reasons"; not for "any CV reasons," but CV-related hospitalizations were provided by sponsor on request	Other; provided by sponsor on request (24 and 52 weeks)[a]	NR at 24 weeks Secondary (52 weeks), as component of composite outcome[a]
Mortality due to any CV reason	Through: • 24 weeks (or 6 months) • 52 weeks (or 12 months)	Safety (24 weeks)[a] NR at 52 weeks	Safety (24 and 52 weeks)[a]	Other; provided by sponsor on request (24 and 52 weeks)[a]	NR at 24 weeks Secondary (52 weeks)[a]

6MWT = 6-minute walk test; CHF = chronic heart failure; CV = cardiovascular; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association; NR = not reported.

[a]These analyses were uncontrolled for multiplicity, so there is an increased risk of erroneously rejecting the null hypothesis.

Sources: Clinical Study Reports, Statistical Analysis Plans, and Protocols for the FAIR-HF,[29] CONFIRM-HF,[30] and AFFIRM-AHF studies;[32] publication, supplementary appendix, and protocol of the HEART-FID study.[31]

NYHA Class

Change in NYHA class was a co-primary end point (at 24 weeks) in the FAIR-HF study, a secondary end point in the CONFIRM-HF study (24 weeks and 52 weeks), and "other" end point in the AFFIRM-AHF study (24 weeks and 52 weeks).

The NYHA functional class system is a subjective but widely used classification used to determine CHF severity based on symptoms, as follows. This particular verbiage is from the protocols of the FAIR-HF and CONFIRM-HF studies, but is generally consistent across included studies and is standardized.[53]

- Class I: Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

- Class II: Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III: Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV: Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

6MWT

The 6MWT was the primary end point of the CONFIRM-HF study at 24 weeks and a secondary end point in the CONFIRM-HF study at 52 weeks and was also a secondary end point in the FAIR-HF study (at 24 weeks) and the HEART-FID study (as a component of the composite primary end point, evaluated at 24 weeks, and as a secondary end point at 52 weeks). Additional time points were also recorded at every visit, although are not reported herein as only the 24-week and 52-week end points were considered to be of interest for this review. The 6MWT is a test of exercise capacity, validated among patients with CHF, that assesses how far a patient can walk along the length of a hard, flat course at their own pace while attempting to cover as much ground as possible in 6 minutes, which was recorded to the nearest metre. According to the protocols of the FAIR-HF and CONFIRM-HF studies, patients were allowed to rest on chairs during the test but were encouraged to resume walking as soon as they felt physically able and were instructed not to perform vigorous activity for 2 hours before the test. In the FAIR-HF and CONFIRM-HF studies, it was specified that every effort was to be made to ensure the test was performed by the same clinic personnel for the duration of the trial for any 1 patient. These additional details were not available in the publications for the HEART-FID study but given that this is a common, simple, and validated assessment, there were no particular concerns that the methodology would greatly vary. The 6MWT was not assessed in the AFFIRM-AHF study.

KCCQ

The KCCQ was reported by the FAIR-HF study (24 weeks), CONFIRM-HF study (24 weeks and 52 weeks), and AFFIRM-AHF study (24 weeks and 52 weeks) as a secondary end point in each case. The KCCQ was not reported in the HEART-FID study. It is a 23-item, self-administered questionnaire that quantifies physical limitation, symptoms (stability, frequency, and burden), self-efficacy, social function, and HRQoL. Scores are transformed to a range of 0 to 100, where higher scores reflect better health status. This outcome was selected with assistance from clinical expert input because it is a disease-specific HRQoL metric. Some studies also reported a generic HRQoL metric, the EQ-5D, which is not detailed here.

Fatigue Score

The change in baseline of self-reported fatigue score was assessed as a secondary end point in the CONFIRM-HF study (24 weeks and 52 weeks) only and was assessed at every visit before patients began the 6MWT assessment. The fatigue score was assessed using a 10-point visual analogue fatigue scale, ranging from 1 for “no fatigue” to 10 for “very severe fatigue.” This outcome was selected for this review with

assistance from clinical expert input and because fatigue is a major symptom of HF and ID and can have a substantial impact on patients' HRQoL.

Serum Ferritin

Serum ferritin was a key factor considered in dosing of FCM in the CONFIRM-HF, HEART-FID, and AFFIRM-AHF studies, and the change in serum ferritin from baseline is available from all 4 included studies at week 24 and/or week 52, depending on study duration. Importantly, serum ferritin is a defining metric of ID, and in the context of HF in particular, ID has been defined as serum ferritin of less than 100 mcg/mL (absolute ID) or less than 300 mcg/mL with TSAT of less than 20% (functional ID).

Hospitalization and Mortality Rate Due to Any CV Reason

Although the treatment goal of FCM in patients with HF and ID is to improve exercise capacity, hospitalizations and mortality due to CV reasons were selected for this review because objective outcomes relating to resource use and mortality are of interest to the committee for deliberation and for the pharmacoeconomic review of FCM. All studies reported some metrics related to hospitalizations and mortality, but rates of hospitalization and death specific to CV reasons were provided by the sponsor at the request of CDA-AMC to facilitate this review, as the preplanned analyses differed in each study. The primary outcome of the HEART-FID study was a hierarchical composite comprising death at 12 months, number of hospitalizations for HF at 12 months, and change from baseline in 6MWT at 6 months; the primary outcome of the AFFIRM-AHF study was the composite of recurrent HF hospitalizations and CV death up to 52 weeks after randomization. These are both described briefly in the hospitalizations section of the results of this report.

Table 9: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
6MWT	The 6MWT is a supervised test that is used to measure the distance a patient can walk on a hard, flat surface over a six-minute period.[54] A specific protocol outlining training, level of support provided to the patient, and standardization of distance available for the patient to walk (30 metres) is provided by the American Thoracic Society.[54]	Construct validity and reliability were examined in patients with chronic HF.[55] **Validity:** The best 6MWD had moderate-to-good correlations with peak exercise capacity (r_s = 0.54 to 0.69) and no-to-fair correlations with body composition, lung function, ejection fraction, and symptoms of anxiety and depression (r_s = 0.04 to 0.49). Patients with higher NYHA classes had lower 6MWD. **Reliability:** The ICC showed good reliability between the 2 6MWTs performed on subsequent days (ICC = 0.90; P < 0.0001). The learning effect was 31 metres (95% CI, 27 metres to 35 metres). Older age (≥ 65 years), lower lung diffusing capacity (< 80% predicted),	The estimated MID in the 6MWT among patients with HF and iron deficiency is 14 metres to 15 metres according to the sponsor's study.[56] Other published data exist suggesting a value of approximately 30 metres as an MID.[57]

Outcome measure	Type	Conclusions about measurement properties	MID
		and higher NYHA class (NYHA class III) were associated with a lower likelihood of a meaningful increase in the second test (odds ratio = 0.45 to 0.56; P < 0.05 for all).	
KCCQ	KCCQ is a 23-item, self-administered questionnaire that quantifies 7 domains: symptom frequency, symptom burden, symptom stability, physical limitations, social limitations, HRQoL, and self-efficacy.[58] Scores are summarized as: (1) TSS, symptom frequency, and symptom burden domains; (2) CSS, physical limitations and TSS; and (3) OSS, physical limitation, TSS, quality of life, and social limitation domains.[58] Scores are transformed to a range of 0 to 100, where higher scores reflect better health status.[58]	**Validity:** In patients with HF, construct validity was supported by showing similar correlations within NYHA class in patients with and without anemia (P for interaction = 0.38).[59] In a pooled analysis of the FAIR-HF and CONFIRM-HF studies, changes in OSS and CSS scores were in conjunction with changes in 6MWT at weeks 12 and 24 in both FCM and placebo arms.[60] **Reliability:** In patients with HF, internal consistency (Cronbach alpha = 0.92 and 0.93 for patients with and without anemia, respectively) and test–retest reliability were similar: mean 3-month change scores in stable patients: –2.8 (SD = 1.4) and –0.5 (SD = 0.8); P = 0.14.[59] **Responsiveness:** In patients with HF, mean 3-month KCCQ change was found to be linearly related to reported health change, with a slope of –2.7 points (95% CI, –3.6 to –1.9) per 1 step down on the Likert scale response.[60] The association was consistent in both patients with and without anemia. Slope estimates: –3.4; 95% CI, –5.0 to –1.8 vs. –2.5; 95% CI, –3.4 to –1.6; P = 0.33.[59]	The estimated MID submitted by the sponsor for KCCQ in patients with HF and iron deficiency was based on the pooled analysis of the FAIR-HF and CONFIRM-HF studies that explored the likelihood of individual improvement or deterioration in KCCQ domains with FCM vs. placebo.[58] Improvements of ≥ 5, ≥ 10, or ≥ 15 points correlate with small, moderate-to-large, or large clinically significant improvements in health status, respectively. A ≥ 5-point deterioration is considered clinically significant worsening.[58] An estimated mean difference of ≥ 2 points to 3 points between treatment groups translates into a clinically relevant improvement in subjective patient well-being.[58] As these are not between-group MIDs, they were not used for the GRADE assessment.
Fatigue	A self-reported tool using a 10-point visual analogue fatigue scale, ranging from 1 for no fatigue to 10 for very severe fatigue.[50]	**Validity:** Validity for the fatigue score in patients with HF has not been established in the literature.[61] **Reliability:** Reliability for the fatigue score in patients with HF has not been established in the literature.[62]	No reported MID for the fatigue score in patients with HF was identified in the literature.
NYHA functional class	Assessments of NYHA functional class were completed by a physician to assess the extent of HF (severity and progression). Higher classification levels indicate more advanced stages	**Validity:** NYHA class is moderately correlated with VO_2 maximum exercise capacity, the Specific Activity Scale, and the 6MWT.[63] Worsening NYHA class appears to correlate well with decreasing 6MWT	No reported MID for the NYHA in patients with HF were identified in the literature.

Outcome measure	Type	Conclusions about measurement properties	MID
	of HF with greater disability and symptoms.[5]	between class II and III, and between class III and IV.[64] In a pooled analysis of the FAIR-HF and CONFIRM-HF studies, improvements in NYHA class were in conjunction with improvements in exercise capacity (measured by 6MWT).[60] **Reliability:** Reliability has not been established in the literature.[63]	

6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; CI = confidence interval; CSS = Clinical Summary Score; FCM = ferric carboxymaltose; HF = heart failure; HRQoL = health-related quality of life; ICC = intraclass correlation coefficient; KCCQ = Kansas City Cardiomyopathy Questionnaire; MID = minimal important difference; NYHA = New York Heart Association; OSS = overall summary score; TSS = Total Symptom Score; vs. = versus.

Statistical Analysis

Sample Size and Power Calculation

FAIR-HF

Sample size calculations were based on the Physician's Global Assessment (PGA) score and change in NYHA class 24 weeks after start of iron repletion. A 2-group t test with a 0.025 two-sided significance level had 90% power to detect a difference in PGA score means of 0.900, assuming that the common SD was 2.407, when the sample sizes in the 2 groups were 134 and 268 (a total sample size of 402). A 2-group t test with a 0.025 two-sided significance level had 90% power to detect a difference in NYHA class means of 0.500, assuming that the common SD was 1.337, when the sample sizes in the 2 groups were 134 and 268 (a total sample size of 402). With an estimated rate of 30% of patients who do not have a week 24 assessment while taking an investigational drug, 576 patients had to be included in the study.

CONFIRM-HF

Using the data reported in the FAIR-HF study, the mean difference in the 6MWT to week 24 was assumed to be 29.1 metres with a SD of 71.8 metres. Based on these assumptions, a sample size of 130 patients per group (260 total) was needed for 90% power using an alpha of 0.05 (2-sided) to detect mean treatment effect of at least 29.1 metres at week 24. The sample size was rounded up to 150 patients per group (300 total) to allow for some loss of information due to early discontinuations.

HEART-FID

With 3,014 patients (1,507 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 estimated 90% power at an overall 2-sided significance level of 0.01 for the primary end point, accounting for 1 interim analysis. Considerations for time to CV death or hospitalization for HF were also included in the power calculations, although will not be detailed here as these time-to-event outcomes were not selected to be of interest.

AFFIRM-AHF

It was anticipated that approximately 35% of patients would sustain either a CV death or at least 1 HF hospitalization, and that 12% of patients would sustain a CV death. It was assumed that the rate ratio between FCM and placebo for the composite of recurrent HF hospitalizations and CV deaths would be approximately 25%, with an assumed dispersion factor (K) of 1. The sample size calculation was done using the formula proposed in the study by Zhu and Lakkis.[65] Assuming a rate of recurrent HF hospitalization and CV death of 0.7 events/year in the placebo group, 1,000 patients (500 per study treatment group) would be required to demonstrate a statistically significant rate ratio of 0.75 with a power of 80% and a 2-sided alpha of 0.05. Taking into account 9% loss to follow-up, a sample size of 1,100 patients (550 per treatment group) was planned.

Statistical Testing

The statistical testing methods as well as covariates and/or baseline values that were included in the statistical models for each outcome are provided in Table 10.

FAIR-HF

In the FAIR-HF study, the co-primary end points were change in NYHA class and change in PGA from baseline to week 24. However, PGA was not selected for this review and so will not be detailed further. For all outcomes assessed at 24 weeks, only the closest assessment obtained within the allowed time window of the week 24 visit was to be used.

The FAIR-HF study tested the overall effect of treatment on NYHA class adjusted for baseline by ordered polytomous regression using treatment and baseline NYHA class (separated into 3 dummy binary variables with NYHA class III being the reference) as covariates. Alpha adjustment was planned using the method of Benjamini-Hochberg. The P values for the 2 tests (P value of the treatment covariate in the ordered polytomous regression for the PGA and NYHA values) were to be ordered in size (p1 ≤ p2, where p1 is the P value of the treatment covariate in the ordered polytomous regression for PGA values, and p2 for NYHA values). p2 would be compared to a significance level of 5%. If p2 was 5% or less, both alternative hypotheses would be proven (represented by H_1 and H_2). If p2 was greater than 5% and p1 was 2.5% or less, the corresponding alternative hypothesis of the smaller P value (H_1) would be proven. Other end points were not adjusted for multiplicity. Details on imputation of missing values can be found in Table 10.

For the secondary end point of 6MWT, the analysis of treatment difference was to be done by comparing the model-adjusted means of the corresponding visit based on a model for repeated measures including terms for treatment, baseline, time, and treatment by time with an unstructured covariance matrix to model the within-patient variability. The method of imputation of missing values for 6MWT differed from NYHA because the intervals for assessment for 6MWT were significantly longer (6-week to 12-week intervals), during which time a patient's health status could change considerably; therefore, a more conservative approach was selected for imputation for patients who had missing values due to hospitalization or death (refer to Table 10). No multiplicity adjustment was described for any secondary outcomes, including 6MWT.

The KCCQ and continuous laboratory metrics were analyzed in the same manner as 6MWT.

CONFIRM-HF

The primary efficacy analyses of the change in 6MWT from baseline to week 24 were conducted using an analysis of covariance, with adjustment for baseline 6MWT distance, hemoglobin level at screening (< 12 g/dL and ≥ 12 g/dL), and pooled country (Russia, Ukraine, Poland, and pooled C [other European countries: Austria, Italy, Portugal, Spain, Sweden, and the UK]). A second analysis of covariance was run to examine the terms of interaction between pooled country and treatment group as well as between hemoglobin level at screening and treatment group. No multiplicity adjustment was described for any primary or secondary outcomes.

The protocol describes that, to account for any potential bias introduced in favour of FCM using the imputation for hospitalizations and deaths (refer to Table 10), the analysis of the 6MWT was repeated using observed cases only. Because there had been a previous incidence of AEs leading to hospitalization in the FCM group of the FAIR-HF study (compared to placebo), assuming this held true in the CONFIRM-HF study, any treatment effect of FCM could be artificially inflated by using the worst nonnull imputation (as it would be disproportionately applied to the placebo arm due to patients missing the 6MWT due to hospitalization). Therefore, for the CONFIRM-HF study, the potential for bias was addressed by analysis of observed cases. Observed cases were also analyzed using last observation carried forward (LOCF) at week 24 and week 52 to demonstrate whether any observed treatment benefit of FCM was driven by patients who withdrew before these time points. These considerations were not applied for other efficacy variables.

For NYHA, analysis of covariance repeated measure models were used for the analysis of the continuous secondary end point variables, and repeated measures polytomous regression for the noncontinuous variables analysis. Time-to-event analyses for outcome-related end points (adjudicated hospitalizations and deaths) were conducted using Kaplan-Meier estimators and log-rank tests. Hazard ratios and corresponding 95% CIs were obtained from the proportional hazard ratio models. For safety outcomes, missing and/or incomplete dates or times for AEs were imputed only for determination of treatment emergence and time of event relative to the first administration of study medication. A worst-case approach was followed in the event of missing severity or causality data.

HEART-FID

The primary outcome follows a hierarchical scale of clinical severity comprising death at 12 months, number of hospitalizations for HF at 12 months, or change from baseline in 6MWT distance at 6 months, and the main comparison was conducted using the Wilcoxon-Mann-Whitney test for the null hypothesis that a randomly chosen patient in the FCM group is equally likely to be ranked better or worse than a randomly chosen patient in the control group. However, the outcomes assessed in this report were provided by the sponsor as absolute between-arm differences upon request and are not subject to this statistical methodology.

With respect to the outcomes assessed in this review, no adjustments for multiplicity were reported in the protocol.

AFFIRM-AHF

The primary outcome was the composite of recurrent HF hospitalizations and CV death up to 52 weeks after randomization, which was assessed using a rate ratio analyzed using a negative binomial model. This was selected over the Poisson distribution because it allows for different individual tendencies with respect to their risks of repeat hospitalizations, according to the trial protocol.

With regards to the secondary outcomes (refer to Table 10), Hochberg procedure was used to control the overall type I error for the evaluation of the secondary end points on FAS at the 2-sided alpha of 5%. All secondary end point P values were sorted from the smallest to the largest and compared with Hochberg critical values. The highest P value with lower value than the Hochberg critical value was chosen. This P value and all lower P values were considered statistically significant at an overall 2-sided level of 5%.

Other end points not listed as secondary end points were not adjusted for multiplicity, such as the change from baseline in NYHA functional class, KCCQ, safety end points, and laboratory values.

In general, there was no replacement for missing data with some exceptions, such as to impute missing date values for time-to-event calculations and for assigning missing dates to AEs and concomitant medications. However, there was otherwise no imputation for missing outcomes data.

Due to the COVID-19 pandemic, sensitivity analyses were to be performed for the primary and secondary end points on the FAS censoring patients at index date. The index date was given by country and corresponds with the first reported patient with COVID-19 in the country. All events after the index date were to be excluded and patient's follow-up time was considered only up to the index date.

Subgroup Analyses

Both the FAIR-HF and CONFIRM-HF studies conducted subgroup analyses on their primary end points across a wide range of baseline demographic and disease-related characteristics. The main purpose of the subgroup analyses was to evaluate the consistency of the treatment effects across the different populations and subgroups. As no subgroups were identified to be of special interest, these will not be described in detail in this report.

In the HEART-FID study, no prespecified subgroup analyses were detailed.

In the AFFIRM-AHF study, no prespecified subgroups were detailed, although additional exploratory analyses of subgroups by baseline characteristics were permitted by the protocol and were conducted for several demographic and disease-related characteristics according to the Statistical Analysis Plan and Clinical Study Report.

Table 10: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
FAIR-HF				
NYHA at week 24 (primary end point)	Ordered polytomous regression	Treatment, baseline NYHA class values (separated into 3 dummy binary variables)	LOCF for patients known to be alive and not hospitalized with at least 1 previous follow-up value available. Patients considered as NYHA class IV if hospitalized, and class V if they had died. Patients without follow-up values were excluded. If a previous follow-up value was imputed to class IV for hospitalization, this value was used for the LOCF imputation.	Analysis repeated on PP set.
6MWT at week 24	Model for repeated measures	Treatment, baseline, time, and treatment by time	No imputation of missing values if patient was known to be alive and not hospitalized. If a patient was hospitalized and unable to exercise, the worst nonnull test across the study (i.e., for all time points and for all patients) was used. If the patient had died, the value was set to 0.	Analysis repeated on PP set.
KCCQ at week 24	Model for repeated measures	Treatment, baseline, time, and treatment by time	LOCF for patients known to be alive and not hospitalized with at least 1 follow-up value available. If dead or hospitalized, the worst reply was be used for the imputation. At least 1 previous follow-up value had to be available. Patients with no follow-up values were excluded.	None
Clinical laboratory evaluations of ferritin	Comparison of the model-adjusted means of the corresponding visit based on a model for repeated measures including terms for treatment, baseline, time,	Treatment, baseline, time, and treatment by time	LOCF method	None

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
	and treatment by time with an unstructured covariance matrix to model the within-patient variability			
Rate of hospitalization for any CV reason and rate of death for any CV reason	The total number of events, the number of patients with at least 1 event, and the event hazard rate per 100 PY "at risk" was tabulated by treatment group. PY at risk of event were taken as the sum of the observation time from start of study treatment until the first occurrence of the event concerned, or until censoring.	None	Not described	Analysis repeated on PP set.
Severe AEs	Simple frequencies	None	No imputation performed on safety analysis	None
CONFIRM-HF				
Change in 6MWT from baseline (week 24, primary end point)	ANCOVA	Baseline 6MWT distance, hemoglobin level at screening, and country	For hospitalized patients, the worst nonnull 6MWT result collected across the study was then used for the analysis. For patients who died, a value of 0 was imputed. No imputation for living patients who were not hospitalized.	Analysis repeated with treatment by country interaction and treatment by baseline hemoglobin added; analysis repeated on the PP set; analysis repeated on the FAS and PP sets with LOCF.
Change in 6MWT from baseline (week 52)	ANCOVA with repeated measures	Treatment, visit, sex, age, geographic region, country, baseline score, and hemoglobin level at screening (< 12 g/dL or ≥ 12 g/dL) as well as a term of interaction between visit and treatment	For hospitalized patients, the worst nonnull 6MWT result collected across the study was then used for the analysis. For patients who died, a value of 0 was imputed	Analysis repeated on the PP set; analysis repeated using LOCF for week 52 without imputation; week 52 analysis using the same approach as described for week 24.
NYHA class (week 24 and week 52)	Repeated measures polytomous regression	Treatment, visit, sex, age, geographic region, country, baseline score, and hemoglobin level at screening (< 12 g/dL or ≥ 12 g/dL) as well as a term of interaction	NYHA class missing values due to patients who died were imputed using the worst possible assessment of class V, and patients hospitalized were attributed a value of	Analysis repeated on the PP set.

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
		between visit and treatment. Adjusted for baseline NYHA class.	class IV. Other missing values were imputed using LOCF.	
KCCQ and fatigue score (week 24 and 52)	ANCOVA with repeated measures	"Where appropriate," terms for treatment, sex, age, and baseline score were included (unclear if this was applied to these outcomes)	Not described	None
Change from baseline to weeks 6, 12, 24, 36, and 52 in clinical laboratory panels (ferritin)	ANCOVA with repeated measures	Treatment, visit, sex, age, geographic region, country, baseline score, and hemoglobin level at screening (< 12 g/dL or ≥ 12 g/dL) as well as a term of interaction between visit and treatment	The LOCF method was used for week 24 and week 52 end points	None
Hospitalization rate (i.e., incidence of all-cause hospitalization, hospitalization due to worsening of CHF, hospitalization due to other CV-related events)	Descriptive as incidence per 100 PY	None	NR	None
Time to first hospitalization (i.e., for any reason, any CV reason, or due to worsening of HF)	Kaplan-Meier estimators and log-rank tests. HRs and 95% CIs were obtained from the proportional hazard ratio models	None	If, at the time of completion or withdrawal, the event of interest had not occurred, the patient was censored at the date of the completion or withdrawal. Missing date values were imputed for time-to-event analyses.	Post hoc sensitivity analyses were conducted on the secondary end point of hospitalization events due to worsening HF using negative binomial regression models where incidence rate ratios between treatment groups the 95% CIs and P values were calculated.
Death rate (i.e., incidence of all-cause death, death due to worsening of CHF, death due to	Incidence per 100 PY	None	NR	None

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
other CV-related events)				
Time to death (i.e., for any reason, for any CV reason, due to worsening HF)	Kaplan-Meier estimators and log-rank tests. HRs and 95% CIs were obtained from the proportional hazard ratio models	None	NR	None
Serious and nonserious AEs	Summary statistics	None	Imputation was used only to determine treatment emergence and the time of the event relative to the first administration of study medication. A worst-case approach was followed in the event of missing severity or causality data. If the severity was missing, “severe” was imputed. If causality data were missing, “related to study treatment” was imputed. In the event that no coding information was available for a specific AE, the AE was presented as “uncoded” in summary tables.	None
HEART-FID				
Hierarchical composite (primary outcome) • Death at 12 months • Hospitalization at 12 months • Change from baseline in 6MWT at 6 months	Wilcoxon-Mann-Whitney test	None	Multiple imputation model with Markov chain Monte Carlo algorithm with the exception of patients unable to complete 6MWT at 6 months (these values were imputed as the worst observed change in 6MWT distance)	Several alternative imputation methods.
Secondary time to first event outcomes (e.g., time to CV death or hospitalization for HF, time to	Cox proportional hazards model	None	NR	None

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
CV death or CV hospitalization, time to CV death or intervention for worsening HF)				
Change from baseline in 6MWT at 12 months	Linear regression adjusting for baseline value of 6MWT distance	None	Refer to the hierarchical composite row	Refer to the hierarchical composite row.
AFFIRM-AHF				
Composite (primary outcome) up to 52 weeks after randomization • Recurrent HF hospitalizations • CV death	Rate ratio (95% CI and P value) Negative binomial model	Based on CEC adjudicated events. Sex, age, HF etiology (ischemic/nonischemic), HF duration (newly diagnosed at index hospitalization or known documented HF before index hospitalization), country, and centre	None	Analysis repeated without adjustment. Analysis repeated using PP set. Confirmatory analysis on FAS population using joint frailty model to analyze repeat hospitalization rate while accounting for associated mortality rate.
Secondary end points (52 weeks) • Composite (recurrent CV hospitalizations and CV deaths) • HF hospitalizations analyzed as recurrent event • CV mortality analyzed as time to first event • Composite HF hospitalizations or CV death as time to first event • Days lost due to HF hospitalizations or CV death	NR	Sex, age, HF etiology (ischemic/nonischemic), HF duration (newly diagnosed at index hospitalization or known documented HF before index hospitalization), country, and centre.	None	Analysis repeated on the PP set.

6MWT = 6-minute walk test; AE = adverse event; ANCOVA = analysis of covariance; CEC = clinical events classification; CHF = chronic heart failure; CI = confidence interval; CV = cardiovascular; FAS = full analysis set; HF = heart failure; HR = hazard ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; LOCF = last observation carried forward; NR = not reported; NYHA = New York Heart Association; PP = per protocol; PY = patient-years.

Source: Clinical Study Reports, Statistical Analysis Plans and Protocols for the FAIR-HF,[29] CONFIRM-HF,[30] and AFFIRM-AHF studies;[32] publication, supplementary appendix, and protocol of the HEART-FID study.[31]

Analysis Populations

The analysis populations of each study are summarized in Table 11. The FAIR-HF and CONFIRM-HF studies are summarized together because their study designs were similar in terms of analysis populations.

Table 11: Analysis Populations of Included Studies

Study	Population	Definition	Application
FAIR-HF and CONFIRM-HF	FAS	All patients randomized to treatment and in whom investigational drug treatment was started. The FAS was analyzed according to the intent-to-treat principle.	The FAS was the main analysis set used for the primary and secondary efficacy analyses.
	PPS	All patients who participated in the study (in the FAS) without major protocol violations, and, in the CONFIRM-HF study, observed cases (without imputation for patients that were hospitalized at the time or had died). Patients who discontinued the investigational drug or the study because of either iron overload or anemia, or patient who died, were not be excluded from the PP analysis set. Patients were analyzed based on the treatment to which they were randomized.	Sensitivity analyses.
	SS	All patients who were started on investigational drug treatment. Patients were analyzed according to the treatment which they received.	Primary analysis set for the safety analysis.
HEART-FID	ITT	All patients randomized to a treatment group of the study regardless of compliance with the study medication.	All primary, secondary, and other end point analyses.
	PPP	Subset of the ITT population excluding patients who complied with the randomized treatment for < 50% of follow-up. In cases of medication error, treatment assignments in the PP analysis were analyzed according to actual treatment received.	Sensitivity analyses.
AFFIRM-AHF	FAS	All randomized patients for whom administration of study treatment was started and who had at least 1 postbaseline visit (including calls), death, or hospitalization, or who withdrew from the study after but not on the randomization date, analyzed as randomized. Patients with protocol deviations concerning inclusion criterion 5 (failure to provide the appropriate written informed consent before any study-specific procedures) were to be excluded from FAS.	Primary, secondary, and other efficacy end points.
	SAF	All randomized patients for whom administration of study treatment was started, analyzed as treated.	Safety end points.
	PPS	All patients in the FAS who had no major protocol violations as defined in the Statistical Analysis Plan.	Sensitivity analyses of the primary, secondary, and other efficacy end points.

FAS = full analysis set; ITT = intent to treat; PP = per protocol; PPP = per-protocol population; PPS = per-protocol set; SAF = safety; SS = safety set.

Source: Clinical Study Reports, Statistical Analysis Plans, and Protocols for the FAIR-HF,[29] CONFIRM-HF,[30] and AFFIRM-AHF studies;[32] publication, supplementary appendix, and protocol of the HEART-FID study.[31]

Results

Patient Disposition

The disposition of patients screened and randomized in each study is summarized in Table 12. There were high proportions of screening failures in the FAIR-HF (51.8%), CONFIRM-HF (48.4%), and HEART-FID (62.6%) studies, primarily due to failing eligibility criteria. At least 70% of enrolled patients completed the study in each case. Discontinuation due to AE was generally uncommon. The PPS in the CONFIRM-HF study was notably smaller than the FAS due to a large number of protocol violations.

Baseline Characteristics

The baseline characteristics outlined in Table 13 (CHF) and Table 14 (AHF) are limited to those that are most relevant to this review or were felt to affect the outcomes or interpretation of the study results.

The mean age across studies and treatment arms ranged from approximately 67 years to 69 years in the CHF studies and was slightly higher in the AFFIRM-AHF study (71 years in the FCM group and 70 years in the placebo group). The proportion of female patients was 44% to 45% in the AFFIRM-AHF study, 45% to 49% in the CONFIRM-HF study, 52% to 55% in the FAIR-HF study, and 33% to 35% in the HEART-FID study in the FCM group and the placebo group, respectively. In all cases, the populations were disproportionately white race, especially in the FAIR-HF study (99.7% and 100% in the FCM group and the placebo group, respectively) and the CONFIRM-HF study (99% and 99% in the FCM group and the placebo group, respectively). In terms of the distribution of NYHA classes, the FAIR-HF study mostly included patients in NYHA class III (> 80% while the remainder were class II at baseline), while in the CONFIRM-HF, HEART-FID, and AFFIRM-AHF studies, the balance was closer to even between class II and class III. The HEART-FID study also included NYHA class IV, and the AFFIRM-AHF study also included class I and class IV, but the proportion of each of these were very low in the respective studies (i.e., ≤ 3%). Comorbidities were common, where reported, especially hypertension, dyslipidemia, diabetes mellitus, and other CV conditions such as atrial fibrillation and history of myocardial infarction.

Table 12: Summary of Patient Disposition

Patient disposition	FAIR-HF		CONFIRM-HF		HEART-FID		AFFIRM-AHF	
	FCM	Placebo	FCM	Placebo	FCM	Placebo	FCM	Placebo
Screened, N	957		589		8,195		[redacted]	
Screening failures, N (%)	496 (51.8)		285 (48.4)		5,127 (62.6)		[redacted]	
Primary reason for screening failure, N (%)								
Failed eligibility criteria	496 (100.0)		271 (95.1)		5,109 (99.6)		[redacted]	
Death	0		0 (0.0)		NR		NR	
Physician decision	0		1 (0.4)		NR		NR	
Withdrawal of consent	0		8 (2.8)		17 (0.2)		[redacted]	

Patient disposition	FAIR-HF		CONFIRM-HF		HEART-FID		AFFIRM-AHF	
	FCM	Placebo	FCM	Placebo	FCM	Placebo	FCM	Placebo
Other	0		5 (1.8)		1 (0.01)[a]			
Randomized, N (%)	304	155	152	152	1,532	1,533	567	565
Completed study			123 (80.9)	128 (84.2)	1,123 (73.3)	1,121 (73.1)		
Discontinued study, n (%)			29 (19.1)	24 (15.8)	409 (26.7)	412 (26.9)		
Reasons for study discontinuation, n (%)								
Adverse event[b]			3 (2.0)	3 (2.0)	NR	NR		
Occurrence of stroke			NR	NR	NR	NR	NR	NR
Incompatible concomitant medication			NR	NR	NR	NR	NR	NR
Death			12 (7.9)	14 (9.2)	354 (23.1)	367 (23.9)	98 (70.0)	95 (74.2)
Lost to follow-up			0 (0.0)	2 (1.3)	7 (0.5)	4 (0.3)	1 (0.7)	1 (0.8)
Physician decision	NR	NR	1 (0.7)	1 (0.7)	NR	NR	0 (0.0)	1 (0.8)
Protocol violation			2 (1.3)	0 (0.0)	NR	NR	6 (4.3)	10 (7.8)
Withdrawal by patient			8 (5.3)	3 (2.0)	48 (3.1)	41 (2.7)	27 (19.3)	
Severe anemia			NR	NR	NR	NR	NR	NR
Other			3 (2.0)	1 (0.7)	NR	NR		
Analysis populations								
FAS, n (%)	304 (99.3)	155 (100.0)	150 (98.7)	151 (99.3)	NR	NR	558 (98.4)	550 (97.3)
PPS, n (%)			119 (78.3)	133 (87.5)	NR	NR		
Safety, n (%)	305 (99.7)	154 (99.4)	152 (100)	152 (100)	NR	NR	559 (98.6)	551 (97.5)

FAS = full analysis set; FCM = ferric carboxymaltose; NR = not reported; PPS = per-protocol set.

[a]Screened in error.

[b]In the FAIR-HF study, the adverse events category was defined as "development of an intolerable AE or pregnancy."

Sources: Clinical Study Reports, Statistical Analysis Plans, and Protocols for the FAIR-HF,[29] CONFIRM-HF,[30] and AFFIRM-AHF studies;[32] publication, supplementary appendix, and protocol of the HEART-FID study.[31]

Table 13: Summary of Baseline Characteristics From Studies Included in the Systematic Review — Chronic Heart Failure

Characteristic	FAIR-HF		CONFIRM-HF		HEART-FID	
	FCM N = 304	Placebo N = 155	FCM N = 150	Placebo N = 151	FCM N = 1,532	Placebo N = 1,533
Age, mean (SD)	67.8 (10.3)	67.4 (11.1)	68.8 (9.5)	69.5 (9.3)	68.6 (10.9)	68.6 (11.2)
Female sex, n (%)	159 (52.3)	85 (54.8)	67 (45)	74 (49)	506 (33)	531 (35)
White race, n (%)	303 (99.7)	155 (100.0)	149 (99)	150 (99)	1,324 (86)	1,325 (86)
NYHA class II, n (%)	53 (17.4)	29 (18.7)	80 (53)	91 (60)	797 (52)	820 (53)
NYHA class III, n (%)	251 (82.6)	126 (81.3)	70 (47)	60 (40)	711 (46)	692 (45)
NYHA class IV, n (%)	NA	NA	NA	NA	22 (1)	19 (1)
LVEF %, mean (SD)	31.9 (5.5)	33.0 (6.1)	37.1 (7.5)	36.5 (7.3)	30.8 (7.0)	30.6 (7.3)
Body mass (kg), mean (SD)	77.0 (14.2)	77.6 (16.3)	78.6 (14.0)	80.8 (18.4)	NR	NR
Body mass index (kg/m^2), mean (SD)	28.0 (4.8)	28.1 (5.1)	28.3 (4.6)	29.1 (5.7)	[redacted]	[redacted]
Systolic blood pressure (mm Hg), mean (SD)	126 (15)	126 (15)	125 (14)	124 (13)	[redacted]	[redacted]
Diastolic blood pressure (mm Hg), mean (SD)	77 (9)	76 (10)	75 (8)	75 (8)	NR	NR
Pulse (beats per minute), mean (SD)	71 (11)	72 (12)	69 (11)	71 (11)	[redacted]	[redacted]
Ischemic cause of heart failure, n (%)	245 (80.6)	123 (79.4)	125 (83)	126 (83)	[redacted]	[redacted]
Hypertension, n (%)	243 (79.9)	128 (82.6)	130 (87)	130 (86)	NR	NR
Dyslipidemia, n (%)	144 (47.4)	70 (45.2)	98 (65)	98 (65)	NR	NR
Diabetes mellitus, n (%)	93 (30.6)	37 (23.9)	38 (25)	45 (30)	[redacted]	[redacted]
Smoking, n (%)	[redacted]	[redacted]	54 (36)	41 (27)	NR	NR
AF, n (%)	94 (30.9)	44 (28.4)	66 (44)	73 (48)	[redacted]	[redacted]

Characteristic	FAIR-HF		CONFIRM-HF		HEART-FID	
	FCM N = 304	Placebo N = 155	FCM N = 150	Placebo N = 151	FCM N = 1,532	Placebo N = 1,533
MI, n (%)	168 (55.3)	90 (58.1)	90 (60)	90 (60)	NR	NR
Angina pectoris, n (%)	171 (56.3)	89 (57.4)	98 (65)	91 (60)	NR	NR
Stroke, n (%)	24 (7.9)	9 (5.8)	21 (14)	24 (16)	NR	NR
Coronary revascularization, n (%)	64 (21.1)	31 (20.0)	46 (31)	39 (26)	NR	NR
Hemoglobin (g/dL), mean (SD)	11.9 (1.3)	11.9 (1.4)	12.37 (1.41)	12.42 (1.30)	NR	NR
MCV (fL)	91.6 (8.1)	91.7 (6.7)	NR	NR	NR	NR
Ferritin (mcg/mL), mean (SD)	52.5 (54.5)	60.1 (66.5)	57.0 (48.4)	57.1 (41.6)	56.0 (47.3)	57.3 (51.4)
Ferritin < 100 mcg/mL, n (%)	NR	NR	136 (91)	133 (88)	NR	NR
TSAT %, mean (SD)	17.7 (12.6)	16.7 (8.4)	20.2 (17.6)	18.2 (8.1)	23.9 (11.2)	23.0 (10.3)
CRP (mg/L), mean (SD)	7.46 (5.34)	9.12 (5.48)	5.19 (9.00)	6.00 (11.60)	NR	NR
BNP (pg/mL), mean (SD)	NR	NR	772 (995)	770 (955)	NR	NR
NT pro-BNP (pg/mL), mean (SD)	NR	NR	2,511 (5,006)	2,600 (4,555)	NR[a]	NR[b]
Sodium (mmol/L), mean (SD)	141 (3)	141 (3)	143 (3)	142 (5)	NR	NR
Potassium (mmol/L), mean (SD)	4.65 (0.61)	4.58 (0.52)	4.69 (0.54)	4.63 (0.55)	NR	NR
ALT (U/L), mean (SD)	20.5 (12.3)	18.8 (8.1)	21.1 (18.9)	18.7 (9.9)	NR	NR
AST (U/L), mean (SD)	23.1 (10.4)	22.4 (7.2)	26.2 (19.6)	23.5 (8.6)	NR	NR
Creatinine (mg/dL), mean (SD)	1.2 (0.6)	1.02 (0.6)	NR	NR	NR	NR
eGFR (mL/min/1.73 m^2), mean (SD)	63.8 (21.2)	64.8 (25.3)	66.4 (21.7)	63.5 (20.9)		

AF = atrial fibrillation; ALT = alanine transaminase; AST = aspartate transferase; BNP = brain natriuretic peptide; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; FCM = ferric carboxymaltose; LVEF = left ventricular ejection fraction; MCV = mean corpuscular volume; MI = myocardial infarction; NA = not applicable; NR = not reported; NT pro-BNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation; TSAT = transferrin saturation.

[a]Median = 1,485.5 pg/mL (interquartile range, 727.1 pg/mL to 3,044.5 pg/mL) from 1,518 patients.

[b]Median = 1,423.6 pg/mL (interquartile range, 710.0 pg/mL to 2,883.8 pg/mL) from 1,526 patients.

Sources: Clinical Study Reports, Statistical Analysis Plans, and Protocols for the FAIR-HF[29] and CONFIRM-HF studies;[30] publication, supplementary appendix, and protocol of the HEART-FID study.[31]

Table 14: Summary of Baseline Characteristics From Studies Included in the Systematic Review — Acute Heart Failure

Characteristic	AFFIRM-AHF	
	FCM N = 558	Placebo N = 550
Age, mean (SD)	71.2 (10.8)	70.9 (11.1)
Female sex, n (%)	244 (44)	250 (45)
White race, n (%)	528 (95)	523 (95)
NYHA class I, n (%)	14 (3)	8 (1)
NYHA class II, n (%)	255 (46)	240 (44)
NYHA class III, n (%)	272 (49)	277 (50)
NYHA class IV, n (%)	16 (3)	22 (4)
LVEF (%), mean (SD)	32.6 (9.6)	32.7 (10.0)
Ischemic cause of heart failure, n (%)	265 (47)	257 (47)
Previous history of heart failure, n (%)	405 (73)	385 (70)
NT pro-BNP (pg/mL), median (IQR)	4,743 (2,781 to 8,128)	4,684 (2,785 to 8,695)
BNP (pg/mL), median (IQR)	1,068 (802 to 1,715)	1,204 (803 to 1955)
Hemoglobin (g/dL), mean (SD)	12.3 (1.6)	12.1 (1.6)
Anemia, n (%)	292 (52)	312 (57)
Ferritin (mcg/mL), mean (SD)	83.9 (62.2)	88.5 (68.6)
Ferritin < 100 mcg/mL, n (%)	408 (73)	380 (69)
TSAT (%), mean (SD)	15.2 (8.3)	14.2 (7.5)
TSAT < 20%, n (%)	457 (82)	469 (85)
eGFR < 60 mL/min per 1.73 m^2, n (%)	292 (52)	288 (52)
Phosphorous (mg/dL), mean (SD)	3.65 (0.727)	3.83 (0.975)

BNP = brain natriuretic peptide; eGFR = estimated glomerular filtration rate; FCM = ferric carboxymaltose; IQR = interquartile range; LVEF = left ventricular ejection fraction; NT pro-BNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation; TSAT = transferrin saturation.

Sources: Clinical Study Report, Statistical Analysis Plan, and Protocol for the AFFIRM-AHF study.[32]

Concomitant medications are detailed for the CHF studies in Table 15 and for the AHF study in Table 16. The studies differed greatly in the selection of concomitant medications reported, which may reflect the different times in which they were conducted. Where reported, use of diuretics and use of beta-blockers were both common (at least 80% across all studies that reported these). The HEART-FID study uniquely reported use of sacubitril-valsartan (approximately 30%) and sodium-glucose cotransporter-2 inhibitors (approximately 8%), and both the HEART-FID and AFFIRM-AHF studies reported use of mineralocorticoid

receptor antagonists (approximately 56% and 66%, respectively), while the FAIR-HF and CONFIRM-HF studies did not.

Table 15: Summary of Concomitant Medications From Studies Included in the Systematic Review — Chronic Heart Failure

Characteristic	FAIR-HF		CONFIRM-HF		HEART-FID	
	FCM N = 304	Placebo N = 155	FCM N = 150	Placebo N = 151	FCM N = 1,532	Placebo N = 1,533
Diuretic, n (%)	280 (92.1)	140 (90.3)	132 (88)	139 (92)	NR	NR
ACE inhibitor, n (%)	NR	NR	116 (77)	118 (78)	NR	NR
ARB, n (%)	NR	NR	34 (23)	37 (25)	NR	NR
ACE or ARB, n (%)	281 (92.4)	141 (91.0)	NR	NR	901 (59)	923 (60)
Digitalis glycoside, n (%)	46 (15.1)	25 (16.1)	29 (19)	40 (27)	NR	NR
Beta-blocker, n (%)	262 (86.2)	129 (83.2)	133 (89)	139 (92)	1,415 (92)	1,418 (93)
Antithrombotic agents, n (%)	NR	NR	142 (95)	144 (95)	NR	NR
Antiplatelet therapy, n (%)	189 (62.2)	97 (62.6)	NR	NR	NR	NR
Anticoagulant therapy, n (%)	67 (22.0)	22 (14.2)	NR	NR	NR	NR
Lipid-lowering therapy, n (%)	142 (46.7)	72 (46.5)	105 (70)	110 (73)	NR	NR
Insulin and analogues, n (%)	27 (8.9)	9 (5.8)	18 (12)	20 (13)	NR	NR
Oral hypoglycemic drug, n (%)	49 (16.1)	22 (14.2)	26 (17)	32 (21)	NR	NR
Sacubitril-valsartan, n (%)	NR	NR	NR	NR	461 (30)	448 (29)
Mineralocorticoid receptor antagonist	NR	NR	NR	NR	858 (56)	847 (55)
SGLT2 inhibitor	NR	NR	NR	NR	118 (8)	111 (7)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; FCM = ferric carboxymaltose; NR = not reported; SGLT2 = sodium-glucose cotransporter-2.

Sources: Clinical Study Reports, Statistical Analysis Plans, and Protocols for the FAIR-HF[29] and CONFIRM-HF studies;[30] publication, supplementary appendix, and protocol of the HEART-FID study.[31]

Table 16: Summary of Concomitant Medications From Studies Included in the Systematic Review — Acute Heart Failure

Characteristic	AFFIRM-AHF	
	FCM N = 558	Placebo N = 550
ACE inhibitor, n (%)	293 (53)	283 (51)
ARB, n (%)	97 (17)	100 (18)
Angiotensin receptor neprilysin inhibitor, n (%)	35 (6)	36 (7)
Mineralocorticoid receptor antagonist, n (%)	376 (67)	352 (64)
Beta-blocker, n (%)	453 (81)	461 (84)
Digitalis glycosides, n (%)	83 (15)	101 (18)
Loop diuretic, n (%)	483 (87)	465 (85)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; FCM = ferric carboxymaltose.
Sources: Clinical Study Report, Statistical Analysis Plan, and Protocol for the AFFIRM-AHF study.[32]

Exposure to Study Treatments

Patient exposure to study treatments is summarized in Table 17. The format of reporting differed by study. Mean doses received in the placebo arms of the CONFIRM-HF and AFFIRM-AHF studies were higher than mean doses in the corresponding FCM arm, presumably because dosing is based on current iron need and patients assigned to the placebo group would typically not be seeing iron repletion as the study went on. In the CONFIRM-HF study, patients had up to 5 administration of study drug or placebo, while in the AFFIRM-AHF study, it was up to 4; these data were not reported in the FAIR-HF or HEART-FID studies, although the median number of administrations in the HEART-FID study was 6. In both the CONFIRM-HF and AFFIRM-AHF studies, which reported these types of data, a much higher proportion of patients assigned to placebo had higher numbers of injections (e.g., 3 injections to 5 injections) compared to patients assigned to FCM, again likely because this was determined based on iron need.

In the HEART-FID study, data were generally not presented in the same format, and so will be summarized here. Overall, [redacted] patients in the FCM group and [redacted] patient in the placebo group did not receive the assigned drug. Dose interruptions (i.e., missed injections) occurred in [redacted] in the FCM group and [redacted] in the placebo group. The median number of injections during follow-up was [redacted] and was the same in both groups. At the day 180 visit, [redacted] in the FCM group who had received the trial drug did not require additional iron replacement therapy at this visit owing to adequate iron indexes and hemoglobin values. Use of IV iron outside the trial protocol occurred in [redacted] in the FCM group and [redacted] in the placebo group.

No subsequent therapies were given in any included study.

Table 17: Patient Exposure in Included Studies

Exposure	FAIR-HF SAS		CONFIRM-HF SAS		HEART-FID SAS		AFFIRM-AHF SAS	
	FCM N = 305	Placebo N = 154	FCM N = 559	Placebo N = 551	FCM N = 1,532	Placebo N = 1,533	FCM N = 559	Placebo N = 551
Study drug exposure								
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Total dose received								
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	2,316.9 mg (1,366.0 mg) FCM	NR	1,351.97 mg (567.872 mg) FCM or equivalent	1,723.68 mg (670.473 mg) FCM or equivalent
Median	[redacted]	[redacted]	1,500.0 mg iron or equivalent	[redacted]	NR	NR	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	500 mg, 3,500 mg iron or equivalent	[redacted]	NR	NR	[redacted]	[redacted]
Total dose planned								
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Compliance								
Mean (SD)	NR	NR	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Median	NR	NR	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Minimum, maximum	NR	NR	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Number of injections, n (%)								
1	NR	NR	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
2	NR	NR	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
3	NR	NR	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
4	NR	NR	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]

Exposure	FAIR-HF SAS		CONFIRM-HF SAS		HEART-FID SAS		AFFIRM-AHF SAS	
	FCM N = 305	Placebo N = 154	FCM N = 559	Placebo N = 551	FCM N = 1,532	Placebo N = 1,533	FCM N = 559	Placebo N = 551
5	NR	NR	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Median	NR	NR	[redacted]	[redacted]	6 injections	6 injections	NR	NR
IQR	NR	NR	[redacted]	[redacted]	4 to 10	4 to 10	NR	NR

FCM = ferric carboxymaltose; IQR = interquartile range; NR = not reported; SAS = safety analysis set; SD = standard deviation.

Sources: Clinical Study Reports, Statistical Analysis Plans, and Protocols for the FAIR-HF,[29] CONFIRM-HF,[30] and AFFIRM-AHF studies;[32] publication, supplementary appendix, and protocol of the HEART-FID study.[31]

Efficacy

NYHA Class

For the FAIR-HF, CONFIRM-HF, and AFFIRM-AHF studies, the distribution of NYHA class at baseline, week 24, and (where applicable) week 56 are reported in Table 18 by treatment group, along with between-treatment ORs for change in NYHA class from baseline. Note that the direction of the ORs varies by study according to how the analysis was performed.

Among patients with CHF, there was an increased odds of being in a lower (better) NYHA class with FCM compared to placebo in both the FAIR-HF and CONFIRM-HF studies at week 24. In the FAIR-HF study, the OR was 2.400 (95% CI, 1.551 to 3.715; P < 0.001) where an OR of greater than 1 indicates a benefit of FCM, and in the CONFIRM-HF study, the OR was [redacted] where an OR of less than 1 indicates a benefit of FCM.

At week 52, in the CONFIRM-HF study there was an increased odds of being in a lower NYHA class with FCM compared to placebo [redacted] where an OR of less than 1 indicates a benefit of FCM compared to placebo.

Among patients with AHF, in the AFFIRM-AHF study, there was insufficient evidence to confirm a difference between the treatment groups at week 52 [redacted].

Sensitivity analyses for NYHA class were conducted in the FAIR-HF and CONFIRM-HF studies by repeating the analysis using the PPS, and the results generally aligned with the FAS analyses presented here in terms of direction and approximate magnitude. Subgroup analyses in the FAIR-HF study based on demographic and disease characteristics were also generally consistent.

Table 18: Efficacy Results — NYHA Class at Week 24 and Week 52

Assessment	FAIR-HF FAS N = 459		CONFIRM-HF FAS N = 301			AFFIRM-AHF FAS N = 1,108		
	Baseline	Week 24	Baseline	Week 24	Week 52	Baseline	Week 24	Week 52
FCM distribution of NYHA class, n (%)								
n with data	304 (100.0)	[redacted]	150 (100.0)	[redacted]	[redacted]	557 (99.8)	[redacted]	[redacted]
n missing	0 (0.0)	[redacted]	0 (0.0)	[redacted]	[redacted]	1 (0.2)	[redacted]	[redacted]
Class I	0 (0.0)	[redacted]	0 (0.0)	[redacted]	[redacted]	14 (2.5)	[redacted]	[redacted]
Class II	53 (17.4)	[redacted]	80 (53.3)	[redacted]	[redacted]	255 (45.8)	[redacted]	[redacted]
Class III	251 (82.6)	[redacted]	70 (46.7)	[redacted]	[redacted]	272 (48.8)	[redacted]	[redacted]
Class IV	0 (0.0)	[redacted]	0 (0.0)	[redacted]	[redacted]	16 (2.9)	[redacted]	[redacted]
Class V (death)	0 (0.0)	[redacted]	0 (0.0)	[redacted]	[redacted]	0 (0.0)	[redacted]	[redacted]
Placebo distribution of NYHA class, n (%)								
n with data	155 (100.0)	[redacted]	151 (100.0)	[redacted]	[redacted]	547 (99.5)	[redacted]	[redacted]
n missing	0 (0.0)	[redacted]	0 (0.0)	[redacted]	[redacted]	3 (0.5)	[redacted]	[redacted]
Class I	0 (0.0)	[redacted]	0 (0.0)	[redacted]	[redacted]	8 (1.5)	[redacted]	[redacted]
Class II	29 (18.7)	[redacted]	91 (60.3)	[redacted]	[redacted]	240 (43.9)	[redacted]	[redacted]
Class III	126 (81.3)	[redacted]	60 (39.7)	[redacted]	[redacted]	277 (50.6)	[redacted]	[redacted]
Class IV	0 (0.0)	[redacted]	0 (0.0)	[redacted]	[redacted]	22 (4.0)	[redacted]	[redacted]
Class V (death)	0 (0.0)	[redacted]	0 (0.0)	[redacted]	[redacted]	0	[redacted]	[redacted]
Odds ratio (95% CI) FCM vs. placebo	NA	2.400 (1.551 to 3.715)[a]	NA	[redacted]	[redacted]	NA	NR	[redacted][c]
P value	NA	< 0.001[a]	NA	[redacted]	[redacted][c]	NA	NR	[redacted]

CI = confidence interval; FAS = full analysis set; FCM = ferric carboxymaltose; HF = heart failure; LOCF = last observation carried forward; NA = not applicable; NR = not reported; NYHA = New York Heart Association; PPS = per-protocol set; vs. = versus.

[a]In the FAIR-HF study, odds ratios and P values for the treatment difference were ordered polytomous regression using treatment and baseline NYHA class (separated into 3 dummy binary variables). Odds ratio > 1 implies a better response for the FCM group.

[b]In the CONFIRM-HF study, the change in NYHA classification at each time point was analyzed using repeated measures polytomous regression as described for noncontinuous variables. Treatment, visit, sex, age, pooled country, baseline score, and hemoglobin level at screening (< 12 g/dL or ≥ 12 g/dL) were included as covariates in the model; a term of interaction between visit and treatment was also included (FAS, PPS). For the analysis of the week 52 end point (using LOCF), the change in NYHA was analyzed with a logistic regression including the same covariates as previously described. Missing NYHA class values were imputed if a patient was hospitalized or had died: a patient was considered as NYHA class IV if the patient was hospitalized at the time of the planned assessment and as NYHA class V if the patient had died. Odds ratio < 1 implies a better response for the FCM group.

[c]Not adjusted for multiple comparisons; there is an increased risk of a false-positive result.

[d]In the AFFIRM-AHF study, odds ratio from the marginal model of ordinal response using the generalized estimating equations method. The following variables are included in the model: treatment, visit, baseline NYHA class, sex, age, HF etiology, HF duration, and country. An independent working correlation structure is used. The odds ratio indicates that the odds of FCM being in lower response. Lower response categories are better for NYHA score. Class V was imputed for patients who died. If the

patient was hospitalized during a visit window, class IV was imputed if no other assessment available in the visit window. The odds ratio for FCM vs. placebo for analysis without imputation of missing NYHA classes was [redacted].

Sources: Clinical Study Reports for the FAIR-HF,[29] CONFIRM-HF,[30] and AFFIRM-AHF studies.[32]

6-Minute Walk Test

Results for the change in 6MWT from baseline among patients with CHF are reported in Table 19 for the FAIR-HF study (week 24 only, secondary end point), the CONFIRM-HF study (week 24 [primary end point] and week 52 [secondary end point]), and the HEART-FID study (week 24 [third component of hierarchical composite primary end point] and week 52 [secondary end point]).

Week 24

In the FAIR-HF study, the mean change from baseline in 6MWT at 24 weeks was [redacted] in the FCM group compared to [redacted] in the placebo group, and the between-group difference was 34.9 metres (SD = 7.8) ($P < 0.001$). Because no 95% CI was presented for the between-group results, additional data were requested from the sponsor, who provided a post hoc analysis of absolute differences on request to inform the GRADE analysis; according to these additional data, the within-group differences were [redacted] and [redacted] metres, respectively, and the between-group difference was [redacted].

In the CONFIRM-HF study primary analysis at week 24, the change from baseline in 6MWT was [redacted] and [redacted] metres in the FCM and placebo groups, respectively. The least squares mean between-group difference was [redacted].

In the HEART-FID study, as a component of the composite primary outcome, the mean change from baseline to 6 months (i.e., 24 weeks) in 6MWT was [redacted] and [redacted] respectively. The least squares mean difference between groups was [redacted] In the FAIR-HF and CONFIRM-HF studies, sensitivity analyses using the PPS did not include reporting of between-group differences, but the within-group changes from baseline were similar to that of the FAS analyses. In the CONFIRM-HF study, the treatment benefit was also consistent across preplanned and post hoc subgroup analyses on demographic and disease-related features, and in a supportive analysis without primary imputation for deaths and hospitalizations. To our knowledge, no sensitivity or subgroup analyses are available from the HEART-FID study specific to the outcomes presented herein.

Week 52

In the CONFIRM-HF study secondary analyses at week 52, the least squares mean between-group difference was [redacted]. Sensitivity analyses using the PPS did not include reporting of between-group differences, but the within-group changes from baseline were similar to that of the FAS analyses; the treatment benefit was also consistent across preplanned and post hoc subgroup analyses on demographic and disease-related features, and in a supportive analysis without primary imputation for deaths and hospitalizations.

In the HEART-FID study secondary analyses at week 52, the mean change [redacted] in the FCM group and [redacted] in the placebo group. Between-group values were not reported numerically, so additional information was requested from the sponsor, in which it was reported that the mean change from baseline to week 52 was [redacted] and [redacted] metres for the FCM and placebo groups, respectively, with a between-arm difference in change from baseline of [redacted] metres.

Table 19: Efficacy Results — Change From Baseline in 6MWT

Assessment	FAIR-HF FAS N = 459		CONFIRM-HF FAS N = 301		HEART-FID FAS N = 3,065	
	FCM	Placebo	FCM	Placebo	FCM	Placebo
Baseline						
n	[redacted]	[redacted]	150	151	1,531	1,531
Mean distance in metres (SD)	[redacted]	[redacted]	288.4 (98.38)	301.8 (96.52)	273.9 (109.7)	274.7 (109.4)
95% CI	NR	NR	[redacted]	[redacted]	NR	NR
Week 24						
n	[redacted]	[redacted]	[redacted]	[redacted]	1,282	1,287
Mean distance in metres (SD)	313.3 [redacted]	277.4 [redacted]	[redacted]	[redacted]	287.859 (110.7185)	286.208 (116.6502)
95% CI	NR	NR	[redacted]	[redacted]	281.792 to 293.925	279.829 to 292.587
Week 24 change from baseline						
Mean change in metres (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Difference in mean change (95% CI)	34.9 (NR)[a,b]		NR (NR)[b]		4.226 (−0.382 to 8.833)	
P value	< 0.001[b,c]		[redacted]		NR[b]	
Week 52						
n	NA		[redacted]	[redacted]	1,140	1,109
Mean distance in metres (SD)	NA		[redacted]	[redacted]	288.735 (111.5648)	292.564 (119.8033)
95% CI	NA		[redacted]	[redacted]	282.252 to 295.218	285.505 to 299.623

Assessment	FAIR-HF FAS N = 459		CONFIRM-HF FAS N = 301		HEART-FID FAS N = 3,065	
	FCM	Placebo	FCM	Placebo	FCM	Placebo
Week 52 change from baseline						
Mean change in metres (SD)	NA		[redacted]	[redacted]	[redacted]	[redacted]
95% CI	NA		[redacted]	[redacted]	1.200 to 9.360	−0.179 to 8.292
Difference of mean change (95% CI)	NA		[redacted]		NR[b]	
P value	NA		NR		NR[b]	

6MWT = 6-minute walk test; ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; FCM = ferric carboxymaltose; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; NA = not applicable; NR = not reported; SD = standard deviation.

[a]SD = 7.8.

[b]Because there was either no numerical point estimate reported, and/or no 95% CI presented with the point estimate for this outcome, additional data were provided by the sponsor upon request to facilitate the GRADE analysis (refer to Table 2 and Table 3 for GRADE analyses and associated data).

[c]Not adjusted for multiplicity.

[d]Least squares mean. Primary analysis of covariance analysis using imputation for hospitalizations and deaths, using pooled country, baseline 6MWT score, and hemoglobin level at screening (< 12 g/dL or ≥ 12 g/dL) as covariates.

Sources: Clinical Study Reports for the FAIR-HF[29] and CONFIRM-HF studies.[30] Publication and supplementary appendix of the HEART-FID study.[31]

Kansas City Cardiomyopathy Questionnaire

Results for the KCCQ overall summary score (range, 0 to 100, where 100 is a better HRQoL) are reported in Table 20 for the FAIR-HF study (for 24 weeks only), and the CONFIRM-HF and AFFIRM-AHF studies at week 24 and week 52.

Week 24

In the FAIR-HF study at week 24, the study treatment effect of FCM was 7 points (SD = 2) greater in change from baseline of KCCQ overall summary score, compared to placebo (P < 0.001). Because there was no 95% CI provided with the point estimate for the FAIR-HF study, additional data were requested from the sponsor, which reported a between-group difference of [redacted] favouring FCM.

In the CONFIRM-HF study at week 24, the least squares mean between-group difference was 1.3 points (95% CI, –1.88 points to 4.57 points; P = 0.41). In the AFFIRM-AHF study, the difference was [redacted].

Week 52

In the CONFIRM-HF study at week 52, the between-group difference was 4.5 points (95% CI, 1.07 points to 7.94 points; P = 0.010), and in the AFFIRM-AHF study, it was 1.44 points (95% CI, –1.45 points to 4.33 points; P = 0.33).

Table 20: Efficacy Results — Change From Baseline in KCCQ (Overall Summary Score, Range, 0 to 100)

Assessment	FAIR-HF FAS N = 459		CONFIRM-HF FAS N = 301		AFFIRM-AHF FAS N = 1,108	
	FCM	Placebo	FCM	Placebo	FCM	Placebo
Baseline						
n	297	151	150	151	535	523
Mean score (SD)	[redacted]	[redacted]	58.96 (17.253)	58.82 (18.657)	38.06 ([redacted])	37.14 ([redacted])
95% CI	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Week 24						
n	[redacted]	[redacted]	125	124	433	434
Mean score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 change from baseline						
n	286	145	125	124	422	413
Mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference of mean change (95% CI)	7 (NR)[a,b,c]		1.3 (–1.88 to 4.57)[c,d]		3.0 (0.3 to 5.6)[c,e]	
P value	< 0.001[f]		0.41[c,d]		0.028[c,e]	
Week 52						
n	NA		114	106	380	388
Mean score (SD)	NA		[redacted]	[redacted]	[redacted]	[redacted]
95% CI	NA		[redacted]	[redacted]	[redacted]	[redacted]
Week 52 change from baseline						
n	NA		114	106	368	370
Mean change (SD)	NA		[redacted]	[redacted]	[redacted]	[redacted]
95% CI	NA		[redacted]	[redacted]	[redacted]	[redacted]

Assessment	FAIR-HF FAS N = 459		CONFIRM-HF FAS N = 301		AFFIRM-AHF FAS N = 1,108	
	FCM	Placebo	FCM	Placebo	FCM	Placebo
Difference of mean change (95% CI)	NA		4.5 (1.07 to 7.94)[c,e]		1.44 (–1.45 to 4.33)[c,f]	
P value	NA		0.010[c,e]		0.329[c,f]	

ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; FCM = ferric carboxymaltose; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; KCCQ = Kansas City Cardiomyopathy Questionnaire; NA = not applicable; NR = not reported; SD = standard deviation.

[a]SD = 2.

[b]Because there was either no numerical point estimate reported, and/or no 95% CI was presented with the point estimate for this outcome, additional data were provided by the sponsor upon request to facilitate the GRADE analysis (refer to Table 2 and Table 3 for GRADE analyses and associated data).

[c]Not adjusted for multiplicity.

[d]Difference in least squares mean from ANCOVA with repeated measures model with treatment, visit, sex, age, pooled country, baseline value, and hemoglobin level at screening (< 12 g/dL or ≥ 12 g/dL) as covariates.

[e]Difference in adjusted mean change. Estimates are from analysis based on mixed-effect model of repeated measures using unstructured covariance matrix: change score = baseline score + treatment + visit + treatment × visit + baseline covariates.

[f]P values for treatment difference at each visit were calculated from the repeated measures analysis model with fixed effects for treatment, time, and treatment by time interaction, baseline as a covariate, using an unstructured covariance matrix to model the within-patient variability, using contrasts.

Sources: Clinical Study Reports for the FAIR-HF,[29] CONFIRM-HF,[30] and AFFIRM-AHF studies.[32]

Fatigue Score

Only the CONFIRM-HF study assessed the change from baseline in fatigue score, ranked on a visual analogue scale from 0 to 10, where 0 implies no fatigue and 10 represents very severe fatigue (refer to Table 21).

Week 24

At week 24, the between-group difference (as least squares mean) in change in fatigue score was –0.6 (standard error = 0.20; 95% CI, –1.00 to –0.23; P = 0.002).

Week 52

At week 52, the between-group difference (as least squares mean) in change in fatigue score was –0.7 (standard error = 0.21; 95% CI, –1.07 to –0.25; P = 0.002).

Table 21: Efficacy Results — Change from Baseline in Fatigue Score (Range, 0 to 10 on VAS)

Assessment	CONFIRM-HF FAS N = 301	
	FCM	Placebo
Baseline		
n	[redacted]	[redacted]
Mean score (SD)	5.49 (1.632)	5.30 (1.739)
95% CI	[redacted]	[redacted]
Week 24		
n	121	120
Mean score (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Week 24 change from baseline		
n	121	120
Mean change (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Difference in mean change (95% CI)	–0.6 (–1.00 to –0.23)[a]	
P value	0.002[a]	
Week 52		
n	112	105
Mean score (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Week 52 change from baseline		
n	110	103
Mean change (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Difference in mean change (95% CI)	–0.7 (–1.07 to –0.25)[a]	
P value	0.002[a]	

ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; FCM = ferric carboxymaltose; NA = not applicable; NR = not reported; SD = standard deviation; VAS = visual analogue scale.

[a]Least squares means are from an ANCOVA with repeated measures model with treatment, visit, sex, age, pooled country, baseline value, hemoglobin level at screening (< 12 g/dL, ≥ 12 g/dL), and interaction between visit and treatment. The following correction was applied for the sites in Spain due to use of different VAS scale (0 to 10, instead of 1 to 10): corrected fatigue score = (0.9 × case report form value) + 1. For sites not in Spain, if the fatigue score was < 1 or > 10, the value was set to missing for the analysis.

Source: Clinical Study Report for the CONFIRM-HF study.[30]

Serum Ferritin

Results for serum ferritin at baseline, week 24, and week 52 are reported for all 4 included studies in Table 22 based on the analyses requested to inform GRADE. No P values were reported.

At baseline, mean serum ferritin values were less than the threshold of 100 mcg/mL that defines ID in the context of HF.

Week 24

At week 24, across all studies, the FCM groups had mean serum ferritin levels of greater than 100 (although note that patients may still have "functional ID" if their TSAT is < 20% and their serum ferritin is 100 mcg/mL to 300 mcg/mL, as previously discussed), while the mean serum ferritin levels in the placebo groups were close to or less than 100 mcg/mL.

In the FAIR-HF study, at week 24, the between-group difference in absolute mean serum ferritin was 311.7 mcg/mL ( ) in the FCM group and 74.2 mcg/mL ( ) at in the placebo group (P < 0.0001).

In the CONFIRM-HF study, between-group values were not reported, but the mean serum ferritin at week 24 was in the FCM group, representing a mean change from baseline of and in the placebo group the mean serum ferritin was representing a change from baseline of . Additional data were provided by the sponsor upon request, in which it was reported that the between-group difference in change from baseline was . Numerical values for serum ferritin were not reported in the HEART-FID study, although graphical representation can be found in the supplementary documents. Additional data were provided by the sponsor upon request, in which it was reported that the between-group difference in change from baseline was at week 24.

In the AFFIRM-AHF study, at week 24, the mean change from baseline was in the FCM group compared to in the placebo group; no between-group differences were reported. Additional data were provided by the sponsor upon request, in which it was reported that the between-group difference in change from baseline was 264.59 mcg/mL at week 24.

Week 52

At week 52, the mean serum ferritin levels in the FCM groups of the CONFIRM-HF, HEART-FID, and AFFIRM-AHF studies were all in excess of 100 mcg/mL but were lower than 300 mcg/mL. The FAIR-HF study was a 24-week study so there are no 52-week values. In the placebo groups, the levels were close to or less than 100 mcg/mL.

In the CONFIRM-HF study, at 52 weeks, between-group values were not reported, but the mean serum ferritin (mcg/mL) at week 52 in the FCM group was representing a change from baseline of and in the placebo group was representing a change from baseline of

Additional data were provided by the sponsor upon request, in which it was reported that the between-group difference in change from baseline was [redacted] at week 52.

Values for serum ferritin were not reported in the HEART-FID study, although graphical representation can be found in the supplementary documents. Additional data were provided by the sponsor upon request, in which it was reported that the between-group difference in change from baseline was [redacted] at week 52.

In the AFFIRM-AHF study, at week 52, the mean change from baseline was [redacted] in the FCM group compared to [redacted] in the placebo group; no between-group differences were reported. Additional data were provided by the sponsor upon request, in which it was reported that the between-group difference in change from baseline was [redacted].

Table 22: Efficacy Results — Change From Baseline in Serum Ferritin (mcg/L)

	FAIR-HF SAS N = 459		CONFIRM-HF FAS N = 301		HEART-FID[a] FAS N = 3,065		AFFIRM-AHF FAS N = 1,108	
Assessment	FCM	Placebo	FCM	Placebo	FCM	Placebo	FCM	Placebo
Baseline								
n	305	154	150	151	1,517	1,526	557	550
Mean (SD)	52.41 (54.460)	60.25 (66.674)	57.01 (48.400)	57.14 (41.598)	55.98 (47.294)	57.33 (51.380)	83.85 (62.147)	88.47 (68.642)
95% CI	NR	NR	[redacted]					
Week 24								
n	[redacted]							
Mean (SD)	[redacted]							
95% CI	[redacted]							
Week 24 change from baseline								
n	[redacted]							
Mean (SD)	[redacted]							
95% CI	[redacted]							
Difference in means (95% CI)[b]	[redacted]							

Assessment	FAIR-HF SAS N = 459		CONFIRM-HF FAS N = 301		HEART-FID[a] FAS N = 3,065		AFFIRM-AHF FAS N = 1,108	
	FCM	Placebo	FCM	Placebo	FCM	Placebo	FCM	Placebo
Week 52								
n	NA		[redacted]					
Mean (SD)	NA		[redacted]					
95% CI	NA		[redacted]					
Week 52 change from baseline								
n	NA		[redacted]					
Mean (SD)	NA		[redacted]					
95% CI	NA		[redacted]					
Difference in means (95% CI)[b]	NA		[redacted]					

CI = confidence interval; FAS = full analysis set; FCM = ferric carboxymaltose; NA = not applicable; NR = not reported; SAS = safety analysis set; SD = standard deviation.

Note: No outcomes in this table were adjusted for multiplicity.

[a]All data from the HEART-FID study for this end point were provided by the sponsor in response to an additional information request to assist in interpretation of the data.[28]

[b]All between-group differences were provided by the sponsor in response to an additional information request to assist in interpretation of the data.[28] No P values were reported.

Sources: Clinical Study Reports for the FAIR-HF,[29] CONFIRM-HF,[30] and AFFIRM-AHF studies.[32] Publication and supplementary appendix of the HEART-FID study.[31] Additional information request for absolute differences results data.[28]

Hospitalization Rate Due to Any CV Reasons

The event rate per 100 patient-years and differences in CV hospitalizations comparing FCM and placebo are presented in Table 23 based on data provided by the sponsor on request for the purpose of this review. Through both 26 weeks and 52 weeks, the between-group difference in event rate per 100 patient-years was lower in the FCM groups than the placebo groups. At week 26, the 95% CI of the CONFIRM-HF study crossed null, but no other 95% CIs did. Up to 26 weeks, the between-group difference in event rate per 100 patient-years for FCM versus placebo was [redacted] in the FAIR-HF study, [redacted] in the CONFIRM-HF study [redacted] in the HEART-FID study, and [redacted] in the AFFIRM-AHF study. Up to week 52, the values were [redacted] in the CONFIRM-HF study, [redacted] in the HEART-FID study, and [redacted] in the AFFIRM-AHF study.

As the analysis of these data was a de novo analysis requested for this review, and the primary outcomes of the HEART-FID and AFFIRM-AHF studies were both composite outcomes including hospitalization-related and death-related components, the preplanned analyses of the primary end points for these 2 studies will be briefly recapped in the following.

In the hierarchical composite primary end point of the HEART-FID study, death had occurred in 131 patients (8.6%) in the FCM group and in 158 (10.3%) in the placebo group at 12 months, there were 297 and 332 total hospitalizations for HF by 12 months in the FCM and placebo groups, respectively, and the mean change in the 6-minute walk distance from baseline to 6 months was 8 metres (SD = 60) and 4 metres (SD = 59), in the FCM and placebo groups, respectively. The unmatched win ratio for the hierarchical composite outcome in the FCM group compared with the placebo group was 1.10 (99% CI, 0.99 to 1.23; P = 0.02). Results of prespecified sensitivity analyses that included different imputation methods was reported to be consistent with those of the primary analysis. Because more than half the patients underwent randomization after March 2020, the censoring of data after the onset of the COVID-19 pandemic would have excluded the majority of follow-up data from the analyses.

In the primary efficacy end point of the AFFIRM-AHF study, which was a composite of recurrent HF hospitalizations and CV deaths up to 52 weeks after randomization, the annualized event RR for FCM versus placebo was 0.79 (95% CI, 0.62 to 1.01; P = 0.059). In the prespecified COVID-19 sensitivity analysis, the annualized event RR for FCM versus placebo was 0.75 (95% CI, 0.59 to 0.96; P = 0.024).

Table 23: Efficacy Results — CV Hospitalizations (FAS)

Parameter	FAIR-HF		CONFIRM-HF		HEART-FID		AFFIRM-AHF	
	FCM	Placebo	FCM	Placebo	FCM	Placebo	FCM	Placebo
Up to 26 weeks								
N								
Total patient-years of follow-up								
Event rate per 100 patient-years[a]								
Event rate per 100 patient-years (95% CI)[b,c]								
Event rate ratio for FCM vs. placebo (95% CI)[c]								
P value[c]								
Difference in event rate per 100 patient-years for FCM vs. placebo (95% CI)[c]								
Up to 52 weeks								
N	NA							
Total patient-years of follow-up	NA							

Parameter	FAIR-HF		CONFIRM-HF		HEART-FID		AFFIRM-AHF	
	FCM	Placebo	FCM	Placebo	FCM	Placebo	FCM	Placebo
Event rate per 100 patient-years[a]	NA		[redacted]		[redacted]		[redacted]	
Event rate per 100 patient-years (95% CI)[b,c]	NA		[redacted]		[redacted]		[redacted]	
Event rate ratio for FCM vs. placebo (95% CI)[c]	NA		[redacted]		[redacted]		[redacted]	
P value[c]	NA		[redacted]		[redacted]		[redacted]	
Difference in event rate per 100 patient-years for FCM vs. Placebo (95% CI)[c]	NA		[redacted]		[redacted]		[redacted]	

CI = confidence interval; CV = cardiovascular; FAS = full analysis set; FCM = ferric carboxymaltose; NA = not applicable; vs. = versus.

No outcomes in this table were adjusted for multiplicity.

[a]The total number of events for all patients in the treatment group divided by the total patient-years of follow-up in that treatment group multiplied by 100. Follow-up duration is equal to time on study. Time on study (weeks) = (last known date – randomization date + 1)/7.

[b]Estimated event rate multiplied by 100.

[c]Negative binomial model not adjusted for covariates. Based on de novo analyses requested from the sponsor to support this review and does not reflect the Statistical Analysis Plan of the studies.

Source: Additional information request for absolute differences results data.[28]

Mortality Rate Due to Any CV Reasons

The event rate and differences in CV mortality comparing FCM and placebo are presented in Table 24 based on data provided by the sponsor on request for the purpose of this review. Through both 26 weeks and 52 weeks, minor and inconsistent differences were observed, with 95% CIs that always crossed null. Through 26 weeks, between groups, the risk difference comparing FCM to placebo was –1.26% (95% CI, –5.24% to 1.26%) in the FAIR-HF study, 1.35% (95% CI, –3.14% to 6.15%) in the CONFIRM-HF study, [redacted] in the HEART-FID study, [redacted] in the AFFIRM-AHF study. Through 52 weeks, the values were [redacted] in the CONFIRM-HF study, [redacted] in the HEART-FID study, and [redacted].

Please refer back to the hospitalizations result section for details on the composite outcomes of the HEART-FID and AFFIRM-AHF studies that included both hospitalization-related and mortality-related end points, and to the Harms section for further discussion of mortality.

Table 24: Efficacy Results — CV Mortality (FAS)

Parameter	FAIR-HF FAS		CONFIRM-HF FAS		HEART-FID FAS		AFFIRM-AHF FAS	
	FCM	Placebo	FCM	Placebo	FCM	Placebo	FCM	Placebo
Up to 26 weeks								
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Died, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alive, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risk difference % (95% CI)[a]	[redacted]		[redacted]		[redacted]		[redacted]	
Up to 52 weeks								
N	NA		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Died, n (%)	NA		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alive, n (%)	NA		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risk difference, % (95% CI)[a]	NA		[redacted]		[redacted]		[redacted]	

CI = confidence interval; CV = cardiovascular; FAS = full analysis set; FCM = ferric carboxymaltose; NA = not applicable.

[a]Risk difference = FCM – placebo; CI represents 95% Miettinen-Nurminen CI.

Source: Additional information request for absolute differences results data.[28]

Harms

Harms data for CHF from the FAIR-HF, CONFIRM-HF, and HEART-FID studies are reported in Table 25, and harms data for AHF from the AFFIRM-AHF study are reported in Table 26.

Adverse Events

In the FAIR-HF study the proportion of patients who experienced at least 1 AE was [redacted] in the FCM group and [redacted] in the placebo group, while in the CONFIRM-HF study the values were 79.6% and 75.7%, respectively. Overall AEs were not reported in the HEART-FID study. In the AFFIRM-AHF study, at least 1 AE was experienced by 357 (63.9%) patients in the FCM group and 360 (65.3%) patients in the placebo group.

Common AEs that occurred in at least 5% of any 1 treatment group across the FAIR-HF and CONFIRM-HF studies included cardiac failure, atrial fibrillation, angina pectoris, bronchitis, respiratory tract infection (viral), nasopharyngitis, influenza, increased blood pressure, hypertension, hypotension, headache, dizziness, and skin or subcutaneous tissue disorders. For the most part, the proportion of patients experiencing these events were relatively similar between treatment groups. Cardiac failure (chronic) appeared to be slightly less common in the FCM group than the placebo group (in the FAIR-HF study: [redacted] versus [redacted] the CONFIRM-HF study: [redacted] versus [redacted]). Common AEs that occurred in at least 5% of either treatment group in the AFFIRM-AHF study included cardiac failure, infections, GI disorders, nervous system

disorders, metabolism and nutrition disorders, renal and urinary disorders, vascular disorders, injury, and musculoskeletal disorders, and were generally similar across groups.

Serious Adverse Events

The proportions of patients who experienced SAEs in the FAIR-HF, CONFIRM-HF, and HEART-FID studies (FCM versus placebo groups) were [redacted], 28.3% versus 34.9%, and 27.0% versus 26.2%, respectively. Reported SAEs that occurred in at least 2% of patients in any 1 treatment group included cardiac failure, acute myocardial infarction, unstable angina, sudden cardiac death, infections and infestations, pneumonia, COVID-19, acute renal injury, and neoplasms benign, malignant, and unspecified. Again, SAEs of cardiac failure — reported generally as “cardiac failure,” or as “acute” or “chronic” cardiac failure TEAEs — appeared to be slightly more common in the placebo groups than the FCM groups.

In the AFFIRM-AHF study, SAEs occurred in 250 of 559 patients (44.7%) in the FCM group and 282 of 551 patients (51.2%) in the placebo group. The most common were cardiac disorders (31.8% and 36.3% in the FCM and placebo groups, respectively), followed by infections and infestations ([redacted] in the FCM and placebo groups, respectively), followed by general disorders and administration site conditions ([redacted] in the FCM and placebo groups, respectively). Other SAEs were less common.

Withdrawals and/or Treatment Discontinuation Due to AEs

In the FAIR-HF study, [redacted] in the FCM group and [redacted] in the placebo group withdrew from the study treatment due to AEs. Reasons leading to withdrawal from the study drug were anemia ([redacted] in the FCM and placebo groups, respectively) and cardiac disorders ([redacted] respectively).

[redacted] from the FCM group discontinued the study due to SAE (GI hemorrhage and renal cyst). In the placebo group, [redacted] discontinued the study due to SAE ([redacted] of cardiac disorder and [redacted] of anemia, basal cell carcinoma, and malignant melanoma in situ).

In the CONFIRM-HF study, 14 patients (9.2%) in the FCM group and 19 patients (12.5%) in the placebo group withdrew from the study due to AEs. The most common AE-related reason for withdrawal from the study drug was cardiac disorders ([redacted]% and [redacted] in the FCM and placebo groups, respectively). Other AEs leading to withdrawal included sudden cardiac death ([redacted] in the FCM group and [redacted] in the placebo group), cardiac death ([redacted] in the FCM group and 0 in the placebo group), neoplasms (2 in the FCM group and 0 in the placebo group), hip fracture (1 in the FCM group and 0 in the placebo group), urticaria (1 in the FCM group and 0 in the placebo group), GI disorders in the placebo group only ([redacted] of gastric ulcer, GI angiodysplasia, and mesenteric vein thrombosis), cerebrovascular accident ([redacted] in placebo group only), and [redacted] each in the placebo group of anemia, staphylococcal sepsis, and acute renal failure.

AEs leading to withdrawal were not reported in the HEART-FID study.

In the AFFIRM-AHF study, TEAEs leading to withdrawal of study treatment and those leading to study discontinuation were reported separately. TEAEs leading to withdrawal of study treatment occurred in [redacted] patients in the FCM group and [redacted] patients in the placebo group; of these,

approximately most were due to cardiac disorders, most commonly cardiac failure (of patients, respectively), while other cardiac disorders leading to treatment discontinuation occurred in patients in each treatment group. Other less common TEAEs leading to treatment discontinuation included deaths, various types of nervous system disorders (such as cerebrovascular accidents in in each treatment group), and in each treatment group of various types of infections and infestations, renal and urinary disorders, increased serum ferritin, and various respiratory disorders. TEAEs that lead to study discontinuation occurred in patients in the FCM group and patients in the placebo group, again most frequently due to cardiac disorders (of patients, respectively) including most commonly cardiac failure ( ), followed by less common instances (patients per treatment group) of other cardiac disorders such as cardiac arrest, various other specified types of cardiac failure, arrythmias, and others. Other TEAEs leading to study discontinuation were more uncommon.

Mortality

In the FAIR-HF study, 5 deaths occurred in the FCM group and 4 in the placebo group ; of these, death in each treatment group occurred after the study period, but was included in the reporting. In the FCM group during the study period patients died due to sudden death, due to ischemic stroke, and due to severe anemia after terminating the study early. In the placebo group during the study period, patients died due to myocardial infarction, pulmonary edema, and sudden death. These deaths were also evaluated as not related to the study drug. In the FAIR-HF study, deaths were also categorized as “all,” “CV,” or “due to CHF worsening”; note that these are not mutually exclusive categories, as CHF worsening is a type of CV death. In these terms, CV deaths occurred of patients in the FCM groups while deaths due to CHF worsening occurred in ; in the placebo group, CV deaths occurred in of patients and deaths due to CHF worsening occurred in In the CONFIRM-HF study, a total of 13 patients (8.6%) in the FCM group and 14 patients (9.3%) in the placebo group died during the study period. The majority of deaths (n = 25) were related to cardiac disorders and cardiac-related TEAEs in other system organ classes (e.g., sudden cardiac death and cardiac death in the category of general disorders and administration site conditions). Two patients in the placebo group died of noncardiac disorders (staphylococcal sepsis and acute renal failure).

In the HEART-FID study, death from any cause occurred in 361 patients (23.6%) in the FCM group and 376 patients (24.5%) in the placebo group (hazard ratio = 0.90; 95% CI, 0.78 to 1.05). The hazard ratio for death from any cause through month 12 was 0.82 (95% CI, 0.65 to 1.05).

In the AFFIRM-AHF study, patients in the FCM group and in the placebo group had TEAEs resulting in death. The majority of deaths were related to cardiac disorders and cardiac-related TEAEs in other system organ classes (e.g., sudden cardiac death and cardiac death in the category of general disorders and administration site conditions).

Notable Harms

There were no reported cases of hypophosphatemia as TEAEs in both the FAIR-HF and CONFIRM-HF studies.

In the FAIR-HF study, transient decreases in phosphate levels were observed in the FCM group and this was reported to be most pronounced at week 4, but there were no clinical consequences, sequelae, or interventions associated with this change. Differences between treatment arms were observed in the percentage of patients with values outside the normal range were observed for phosphate during follow-up [redacted] in the FCM group versus [redacted] in the placebo group placebo; P = 0.008).

In the CONFIRM-HF study, the minimum recorded serum phosphorus value was [redacted] in 2 patients (1 in the FCM group and 1 in the placebo group), where hypophosphatemia is typically defined as less than 2.5 mg/dL. Among all patients, [redacted] experienced severe hypophosphatemia based on the clinical events classification threshold of 0.3 mmol/L to less than 0.6 mmol/L, although the investigators did not report these as TEAEs.

The overall incidence of hypophosphatemia was not reported in the HEART-FID study, but 1 SAE of hypophosphatemia reportedly occurred in 1 patient in the FCM group and none in the placebo group. This hypophosphatemia event was considered by the investigator to be unrelated to FCM; the event resolved and FCM was continued.

In the AFFIRM-AHF study, there were [redacted] of hypophosphatemia observed, [redacted] of which was in the FCM group and [redacted] was in the placebo group. These were judged as unrelated to the study treatment by the investigators.

Table 25: Summary of Harms Results in CHF (FAIR-HF, CONFIRM-HF, and HEART-FID)

AEs	FAIR-HF		CONFIRM-HF		HEART-FID	
	FCM N = 305	Placebo N = 154	FCM N = 152	Placebo N = 152	FCM N = 1,532	Placebo N = 1,533
AEs, n (%)						
≥ 1 AE	[redacted]	[redacted]	121 (79.6)	115 (75.7)	NR	NR
Most common TEAEs (≥ 5% in any treatment group)						
Cardiac failure chronic	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Cardiac failure	NR	NR	[redacted]	[redacted]	NR	NR
Atrial fibrillation	NR	NR	[redacted]	[redacted]	NR	NR
Angina pectoris	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Bronchitis	NR	NR	[redacted]	[redacted]	NR	NR
Respiratory tract infection viral	NR	NR	[redacted]	[redacted]	NR	NR
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Blood pressure increased	NR	NR	[redacted]	[redacted]	NR	NR
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR

AEs	FAIR-HF		CONFIRM-HF		HEART-FID	
	FCM N = 305	Placebo N = 154	FCM N = 152	Placebo N = 152	FCM N = 1,532	Placebo N = 1,533
Hypotension	NR	NR	[redacted]	[redacted]	NR	NR
Headache	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Dizziness	NR	NR	[redacted]	[redacted]	NR	NR
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
SAEs (≥ 2% in any treatment group)						
Patients with ≥ 1 SAE	[redacted]	[redacted]	43 (28.3)	53 (34.9)	413 (27.0)[a]	401 (26.2)[a]
Cardiac failure	NR	NR	[redacted]	[redacted]	NR	NR
Cardiac failure chronic	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Cardiac failure acute	NR	NR	[redacted]	[redacted]	NR	NR
Acute myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Angina unstable	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Sudden cardiac death	NR	NR	[redacted]	[redacted]	NR	NR
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Pneumonia	NR	NR	[redacted]	[redacted]	57 (3.7)	35 (2.3)
COVID-19	NR	NR	NR	NR	39 (2.5)	37 (2.4)
Renal injury acute	NR	NR	NR	NR	46 (3.0)	40 (2.6)
Neoplasms benign, malignant, and unspecified	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Patients who stopped treatment due to AEs, n (%)						
Patients with ≥ 1 AE leading to study drug withdrawal	[redacted]	[redacted]	14 (9.2)	19 (12.5)	NR	NR
Deaths, n (%)						
Patients who died	5 [redacted]	4 [redacted]	[redacted]	[redacted]	361 (23.6)	376 (24.5)
AEs of special interest, n (%)						
Hypophosphatemia	[redacted]	[redacted]	[redacted]	[redacted]	1 (0.1)[c]	0[c]

AE = adverse event; CEC = clinical events classification; CHF = chronic heart failure; CSR = Clinical Study Report; FCM = ferric carboxymaltose; NR = not reported; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a]During the treatment period (i.e., not the subsequent follow-up period). Through the entire follow-up period, SAEs occurred in 581 patients (37.9%) in the FCM group and in 537 patients (35.0%) in the placebo group.

[b]Not reported by investigators as TEAEs, but were identified in the Clinical Study Report based on laboratory values compared against CEC thresholds for severe hypophosphatemia.

[c]This value reflects serious events only. The number of total events may be higher but was not reported.

Sources: Clinical Study Reports for the FAIR-HF[29] and CONFIRM-HF studies;[30] supplementary appendix the HEART-FID study.[31]

Table 26: Summary of Harms Results in AHF (AFFIRM-AHF)

AEs	FCM N = 559	Placebo N = 551
AEs, n (%)		
≥ 1 AE	357 (63.9)	360 (65.3)
Most common TEAEs (≥ 5% in any treatment group)		
Cardiac disorders[a]	224 (40.1)	244 (44.3)
Cardiac failure	[redacted]	[redacted]
Infections and infestations[a]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders[a]	[redacted]	[redacted]
Gastrointestinal[a]	[redacted]	[redacted]
General disorders and administration site conditions[a]	[redacted]	[redacted]
Nervous system disorders[a]	[redacted]	[redacted]
Metabolism and nutrition disorder[a]	[redacted]	[redacted]
Renal and urinary disorders[a]	[redacted]	[redacted]
Vascular disorder[a]	[redacted]	[redacted]
Injury, poisoning, and procedural complications[a]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders[a]	[redacted]	[redacted]
SAEs (≥ 2% in any treatment group)		
Patients with ≥ 1 SAE	250 (44.7)	282 (51.2)
Cardiac disorders[a]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Cardiac failure acute	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]
Infections and infestations[a]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
General disorders and administration site conditions[a]	[redacted]	[redacted]
Death	[redacted]	[redacted]
Nervous system disorders[a]	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders[a]	[redacted]	[redacted]
Injury, poisoning, and procedural complications[a]	[redacted]	[redacted]

AEs	FCM N = 559	Placebo N = 551
Patients who stopped treatment due to AEs, n (%)		
Patients who stopped treatment	[redacted]	[redacted]
Patients who withdrew from the study due to AEs, n (%)		
Patients who withdrew from the study	[redacted]	[redacted]
Deaths, n (%)		
Patients who died	[redacted]	[redacted]
AEs of special interest, n (%)		
Hypophosphatemia	[redacted]	[redacted]

AE = adverse event; AHF = acute heart failure; FCM = ferric carboxymaltose; NR = not reported; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a]Because individual event types were uncommon to rare, some higher-level categories were included in this table to provide context on the types of AEs experienced by patients.

Source: Clinical Study Report the AFFIRM-AHF study.[32]

Critical Appraisal

Internal Validity

The overall risk of bias with regards to internal validity was low for the randomization process and allocation concealment. Speaking to internal validity only, there were no concerns with regards to between-group imbalances in patient baseline characteristics.

With regards to maintenance of blinding, procedures to maintain blinding were described consistently and appeared appropriate in the FAIR-HF, CONFIRM-HF, HEART-FID, and AFFIRM-AHF studies, such as visual barriers to prevent patients from observing the colour of the injectable solution, and the assignment of blinded and nonblinded staff to handle separate aspects of the protocol. Therefore, the risks of performance and detection bias were considered low. Subjective and patient-reported outcomes may be associated with an increased risk of bias in an open-label setting or in the case of accidental unblinding, but this was considered to be unlikely in these studies.

There was a high percentage of missing data across most outcomes in all 4 of the studies before imputation.

For NYHA in the FAIR-HF and CONFIRM-HF studies, imputation for missing data for patients known to be alive and not hospitalized was done using LOCF, and values for hospitalized patients were imputed as class IV, and dead patients as class V. This was considered to be appropriate in that it accounts for the fact that hospitalized or deceased patients may likely be in a worse CV-related health state as outlined by the NYHA, if they had been able to complete the assessment. In the FAIR-HF study, the percentage of missing patient data at week 24 was low ([redacted] but in the CONFIRM-HF study, the percentage of missing patient data ranged from [redacted] in the week 24 and week 52 end points. These numbers are presumably after imputation was conducted, so it is unclear why the data are missing. In the AFFIRM-AHF study, no imputation for missing NYHA data was described, and at week 52, [redacted] of FCM patients and [redacted]

of the placebo group patients were missing; therefore, there may be an increased risk of bias due to the unknown impact that this missing data may have.

The percentage of missing data for 6MWT ranged from [redacted] in the 24-week outcomes and [redacted] in the 52-week outcomes before any imputation. In the FAIR-HF and CONFIRM-HF studies, imputation methods appeared appropriate: patients hospitalized were assigned the worst nonnull value observed (which, although described as conservative, is somewhat arbitrary and it is difficult to predict how it might impact the results), and dead patients were given a distance score of 0. In the FAIR-HF study, there was no imputation for other missing values, while in the CONFIRM-HF study, the LOCF method was used. In the HEART-FID study, imputations for those who did not perform a test or died before 180 days were imputed as 0 metres, and any missing baseline 6MWT values were imputed as the mean; this is in regards to the primary analysis (i.e., of which 6MWT at 24 weeks was a component of the composite), and it is unclear what was done at 52 weeks.

The outcome of fatigue (assessed in the CONFIRM-HF study) had a similarly high proportion of missing data at week 24 and week 52, and no reported imputation methods; therefore, there is a risk of bias as it may stand to reason that patients with missing data due to poorer health states (e.g., hospitalization or death) may also have been more fatigued had they been able to complete the assessment. Similarly, there was no imputation for the large amount missing data in the KCCQ in the AFFIRM-AHF study, which at week 24 was nearly [redacted], and at week 52 was over [redacted]. Patients unable to complete the KCCQ assessment as a result of poorer health or death would likely have had poorer HRQoL. In the FAIR-HF study, the missing data for KCCQ were relatively low ([redacted]) and in the CONFIRM-HF study it reached nearly [redacted], but in the FAIR-HF study, imputation was undertaken to account for hospitalization (worst nonnull value, which again is somewhat arbitrary) and death (assigned a value of 0). In the FAIR-HF study for this outcome after imputation, at 24 weeks, for placebo there were [redacted] nonmissing values, [redacted], while for FCM there were [redacted] nonmissing values, [redacted] imputed values. No imputation was described for this outcome in the CONFIRM-HF study, and so there is an elevated risk of bias.

Although there was also a substantial proportion of missing data for serum ferritin, it was not expected to cause elevated risk of bias in terms of the direction of effect because it is reasonable to suggest that serum ferritin would not immediately be correlated with whether a patient is hospitalized or dead in this population. Nonetheless, there is potential uncertainty with regards to the magnitude of effect as a result and it is unclear why there were missing data.

For CV hospitalizations, there may have been a risk of bias caused by patients missing due to deaths.

Finally, there did not appear to be any concerns regarding missing data for CV deaths across the included studies.

In supportive analyses of the CONFIRM-HF study using the PPS, the sample size was substantially reduced from the FAS, suggesting there may have been a higher number of protocol violations. The proportion of

patients with any major protocol deviation was [redacted] in the FCM group and [redacted] in the placebo group, for a total of [redacted] across both groups. The Clinical Study Report described that given the majority of patients in the FCM group ([redacted] required only [redacted] of the study drug, compared to [redacted] of placebo (because injection need was determined based on serum ferritin), there was a higher risk of patients being out of compliance (based on a percentage of received versus planned doses) in the FCM group, and indeed there were [redacted] with protocol-violating noncompliance compared to [redacted] the placebo group. There were major protocol deviations in [redacted] in the FCM group related to inclusion criteria ([redacted] for screening ferritin and TSAT; [redacted] for requirement of stable CHF with optimized background therapy) compared [redacted] in the placebo group related to inclusion reasons, and [redacted] related to exclusion reasons (history of ESA, IV iron therapy, and/or blood transfusion in past 6 weeks). Altogether, this may result in a risk of bias due to deviations from the intended interventions. Protocol violations also included patients who missed their baseline dose of the study drug. This issue with a largely reduced PPS relative to the FAS did not appear to be as significantly present in the other studies.

The studies included outcomes that were relevant to the assessment of FCM in this patient population for assessing functional class, exercise capacity, HRQoL, objective outcomes such as hospitalization and death, and other harms-related data. Among the efficacy outcomes, the NYHA and 6MWT were considered the most relevant to the stated treatment goal of FCM (i.e., reduction of symptoms and improvement in exercise capacity). Both the NYHA and 6MWT are commonly used, standardized assessments with evidence of validity and reliability (refer to Table 9). The KCCQ, a disease-specific tool used to assess HRQoL, is not used in clinical practice but does have evidence of validity, reliability, and responsiveness in HF. The fatigue score was assessed in the CONFIRM-HF study; however, has no published evidence regarding validity, reliability, or responsiveness in HF.

Hospitalization rate and mortality are objective measures, and the target of assessment in GRADE was any difference. These outcomes were assessed based on ad hoc analyses the sponsor performed at the request of CDA-AMC to assist in conducting this review, and so statistical and methodological information described about hospitalization and mortality outcomes may or may not apply to the values used in the GRADE table.

Generally, only the primary outcomes — and in some cases, such as in the HEART-FID study, the top secondary outcomes — were adjusted for multiplicity in the included studies. With regards to the outcomes assessed in this review, the primary efficacy analyses of the FAIR-HF study (i.e., NYHA class) and the CONFIRM-HF study (i.e., 6MWT) were adjusted for multiplicity, but other outcomes from these studies were not. In the HEART-FID study, because the primary and top secondary outcomes were all composites that were not considered to be of interest in the review, all of the extracted data informing the reported outcomes herein are based on assessments that were not adjusted for multiplicity. Similarly, in the AFFIRM-AHF study, the primary composite outcome considers multiplicity, but all outcomes assessed in this review lack any multiplicity adjustment. The analyses that are unadjusted for multiplicity are at increased risk of falsely rejecting the null hypothesis.

External Validity

Most critically, the external validity and applicability of the results of this review are limited by the absence of any direct or indirect evidence comparing FCM with other IV iron preparations, which are its direct comparators in patients with HF and ID despite having no specific indication among the HF population. The clinical expert consulted by CDA-AMC, as well as well-established Canadian, European, and American treatment guidelines[4,25-27] all underscore that iron repletion in patients with HF is currently (and generally should be) done with IV formulations due to poor absorption, low doses, and other issues associated oral iron supplementation that are especially critical in the setting of HF, which itself causes physiological differences that limit oral iron efficacy. All 4 studies enrolled patients with diagnosed HF and ID and compared iron supplementation to a complete absence of iron supplementation (and placebo). No conclusions can be drawn from any of the submitted evidence on the relative efficacy or safety of FCM with any other available IV iron formulation in patients with HF and ID.

Additionally, the dose of FCM at each administration visit as well as the method of calculating total iron need per patient differed by study. In particular, the study protocol of the FAIR-HF study had a lower dose of FCM administered at each visit to patients compared to the other studies, as well as compared to the product monograph recommendations. Although the study does still show benefit of FCM in a similar magnitude to the CONFIRM-HF study, there may be generalizability concerns with regards to whether the prevalence of any dose-dependent AEs would be reflective of real-world practice.

With regards to patient populations, with some exceptions that are detailed in the following, the studies were considered by the clinical expert to be generally representative of the patient population with HF living in Canada in terms of age, and most other baseline parameters. However, demographically, the proportion of patients identified as white race was disproportionately high across the trials, particularly in the FAIR-HF and CONFIRM-HF studies (98% to 100% across the treatment arms) but this was also generally true in the other 2 studies (85% and 95%). Whether these results are generalizable to other races is therefore highly uncertain. Additionally, the trials were primarily conducted in countries other than Canada, and so demographic features as well as clinical practice related to both ID and HF individually and together may differ.

The sex distribution in the studies also differed from one another, and in some cases, from the expected distribution in Canadian clinical practice. The clinical expert consulted by CDA-AMC noted that one would generally expect a higher proportion of female than male patients in a cohort of patients with HF and ID, because female patients generally live longer on average (i.e., which interacts with older age being a risk factor for HF) and because female sex is an independent risk factor for ID. In some studies, there were more females than males, but in others, the opposite was true for unknown reasons. Moreover, the patients enrolled in the FAIR-HF and CONFIRM-HF studies were older on average than the other studies, and the older studies (the FAIR-HF, CONFIRM-HF, and AFFIRM-AHF studies) differed in the concomitant medications compared to the HEART-FID study, a more recent study. The potential concerns for generalizability caused by this difference in demographic factors of the patient population is unknown in terms of both direction and magnitude.

Two of the included studies (FAIR-HF and CONFIRM-HF) are relatively old, and standard of care might have changed since their publication; therefore, we cannot confirm whether the results would be replicated with today's standard of care.

Given that the proposed reimbursement request and indication is for patients with NYHA class II or class III, the eligibility criteria of the studies around NYHA class also warrants some discussion. The AFFIRM-AHF study differed from the other 3 included studies in that it enrolled patients with AHF and a broader range of NYHA classes (I to IV inclusive), and the HEART-FID study in patients with CHF also enrolled patients with NYHA class IV. However, the number of patients with NYHA class I and/or class IV was proportionally very low in both studies, so this was not expected to present any appreciable complication in interpretation of the evidence. In real-world practice, treatment decisions are based on clinical practice guidelines around the management of HF with ID, which at this time do not specify limiting iron replacement therapy to patients with NYHA class II and class III. The proposed criteria and populations of the studies therefore may not wholly reflect the diversity of patients currently considered appropriate for IV iron supplementation in the context of HF and ID.

The studies were reflective of the setting in which FCM would be administered (i.e., hospital settings). Some of the key outcomes, such as NYHA class and 6MWT, are common assessments that may be done in clinical practice, while others are tools of clinical trials that may not directly be used in practice (e.g., KCCQ, fatigue score).

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform the CDA-AMC expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.[66,67]

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate — the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. We use the word "likely" for evidence of moderate certainty (e.g., "X intervention likely results in Y outcome").
- **Low certainty**: Our confidence in the effect estimate is limited — the true effect may be substantially different from the estimate of the effect. We use the word "may" for evidence of low certainty (e.g., "X intervention may result in Y outcome").
- **Very low certainty**: We have very little confidence in the effect estimate — the true effect is likely to be substantially different from the estimate of effect. We describe evidence of very low certainty as "very uncertain."
- For RCTs: Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. Studies that enrolled patients with CHF were considered separately from those that enrolled patients with AHF.

Results of GRADE Assessments

Table 2 presents the GRADE summary of findings for FCM versus placebo in patients with CHF and ID, while Table 3 presents these findings for AHF and ID.

Long-Term Extension Studies

No long-term extension studies in the HF population were submitted.

Indirect Evidence

No indirect evidence in the HF population was submitted.

Studies Addressing Gaps in the Systematic Review Evidence

Summary and critical appraisal of meta-analysis by Ponikowski and colleagues.[33]

Objective

The objective of the meta-analysis was to evaluate the effects of FCM treatment on clinical events, such as hospitalizations and mortality, in patients with HF and ID using patient-level data from randomized, placebo-controlled trials of FCM that enrolled adults with HF and ID.

Methods

Inclusion Criteria

Ponikowski and colleagues performed a pooled analysis of patient-level data from trials that met the following criteria: studied adult patients with HF and ID (defined as ferritin < 100 mcg/mL or ferritin 100 mcg/mL to 300 mcg/mL and TSAT < 20%); used FCM as an active treatment for ID; were double-blind, randomized, placebo-controlled trials; had at least 52 weeks of follow-up; and prospectively recorded clinical outcomes (e.g., first and recurrent HF and CV hospitalizations, CV death, and all-cause death).

Included Studies

The meta-analysis ultimately included the CONFIRM-HF, AFFIRM-AHF, and HEART-FID studies. Searches were conducted to identify any additional studies, but none were added per the eligibility criteria. The authors were able to access individual patient data for the included studies.

End Points

The prespecified co-primary efficacy end points were:

- a composite of recurrent (total) CV hospitalizations and death for any CV reason (CV death)
- a composite of recurrent (total) HF hospitalizations and CV death.

All of these outcomes were based on events adjudicated independently by blinded event committees. All 3 FCM trials used consistent criteria for adjudication, which were prespecified in each trial.

The key secondary efficacy end points were time to first CV hospitalization or CV death; time to first HF hospitalization or CV death; rate of total HF hospitalizations; time to first HF hospitalization; time to CV death; time to all-cause death; total CV hospitalizations; time to CV death; time to all-cause death; total CV hospitalizations; time to first CV hospitalization; and total all-cause hospitalizations.

All primary and key secondary end points were examined through 52 weeks of follow-up (primary end points were set with a time window up to 408 days).

Data Analysis

Efficacy analyses were conducted on the full analysis population defined as all randomly assigned patients who received at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment. The safety population comprised all patients who were randomly assigned and received at least 1 dose of study medication, and was used to assess baseline characteristics and analyze the frequency of AEs.

A negative binomial regression model was used to analyze event rates, including recurrent hospitalizations. The models were adjusted for baseline hemoglobin and region as fixed effects. Study was included as a random effect. The between-trial heterogeneity was explored by including a treatment by study interaction and a Cochrane Q test. Time-to-event outcomes used Cox proportional hazard analyses and the models were adjusted for hemoglobin at baseline and region. To explore between-trial heterogeneity, the study effect was included as a fixed effect.

Several preplanned subgroup analyses and sensitivity analyses were conducted. As the purpose of the sponsor presenting this meta-analysis was in part to discuss the impact of TSAT on efficacy results, the TSAT subgroup will be discussed briefly in this subgroup, but other subgroups will not be.

A sensitivity analysis incorporating the IRONMAN trial (which did not include FCM) was also conducted to evaluate IV iron products versus placebo, which will not be discussed in depth here. An additional sensitivity analysis was also conducted using all available follow-up data (i.e., beyond 52 weeks).

Results

Efficacy

The results were in favour of FCM without the 95% CI overlapping null for the co-primary composite end point of CV death and total CV hospitalizations (rate ratio = 0.86; 95% CI, 0.75 to 0.98; P = 0.029). Similarly FCM was associated with a 17% relative rate reduction in total CV hospitalizations (rate ratio = 0.83; 95% CI, 0.73 to 0.96; P = 0.009) and a 16% relative rate reduction in total HF hospitalizations (rate ratio = 0.84; 95% CI, 0.71 to 0.98; P = 0.025). For the outcome of total HF hospitalizations and CV death, the result was in favour of FCM; however, the 95% CI overlapped null (0.75 to 1.01). For the outcome of time to CV death, the 95% CI also crossed null more indicating that there was no statistically significant difference between the treatment arms. Similarly, there was no statistically significant difference for time to all-cause death.

Rate reductions in the primary composite end points were mainly driven by the treatment effect on HF hospitalizations and CV hospitalizations, with no apparent effect on CV or all-cause mortality.

In terms of subgroup results, there was a significant interaction effect identified between TSAT tertile and the composite of CV hospitalization and CV death (interaction P = 0.019) and between TSAT tertile and CV death (interaction P = 0.035), where patients in a lower TSAT tertile were more likely to see treatment benefit than those in a higher TSAT tertile. Although not statistically significant, a similar pattern was observed for the effect of TSAT on total HF hospitalizations and CV death (interaction P = 0.095). There were some other subgroups identified regarding “numerically” different treatment effects by subgroup (e.g., across hemoglobin tertiles and HF etiology); other than these, the effects of FCM therapy on both of the primary efficacy end points, CV death, and all-cause death were similar across other subgroups examined.

Safety

The incidences of investigator-reported serious TEAEs, serious TEAEs leading to death, and serious TEAEs leading to study discontinuation were similar across treatment groups through week 52. No deaths were judged to be the cause of serious treatment-related TEAEs. The rates of serious treatment-emergent infections were 9.9 per 100 patient-years and 9.6 per 100 patient-years in the FCM and placebo groups, respectively. Treatment appeared to be safe and well tolerated.

Critical Appraisal

The meta-analysis appears to be conducted appropriately. All of the included trials were placebo-controlled, double-blind, randomized phase III or phase IV trials in adults with HF and ID. The CONFIRM-HF study was focused on clinical efficacy outcomes such as exercise capacity and NYHA class, although the study did report survival and HF or CV-related outcomes as well. The AFFIRM-AHF and HEART-FID studies were focused primarily on composite outcomes related to hospitalizations and death. All 3 trials were at least 12 months in duration. The studies differed in minor ways with regards to inclusion criteria, such as whether NYHA class I or class IV was included; in the CONFIRM-HF study, only class II and class III were included, while the HEART-FID study additionally included class IV and the AFFIRM-AHF study did not specify any exclusions based on NYHA class. This was not expected to represent an important difference in patient populations, in part because prescription of IV iron is not dependent on NYHA class and in part because very few patients outside of class II and class III were included in any study overall. There were also minor differences with regards to the upper limit of LVEF and the range of included hemoglobin levels, but altogether these were considered very similar. The definitions of ID were the same across the studies.

A key difference in study design is that the AFFIRM-AHF study required patients to be hospitalized for AHF during enrolment, while the CONFIRM-HF and HEART-FID studies required a hospitalization within the prior year (or, in the case of the HEART-FID study, hospitalization within prior the 12 months or elevated N-terminal-pro-brain natriuretic peptide within 90 days of randomization). These differences are important to consider when interpreting the results but were not expected to pose a concern with regards to conducting a meta-analysis such as that presented in the meta-analysis by Ponikowski and colleagues, and all of the studies do represent the patient population in question. The inclusion of the AFFIRM-AHF study, which involves hospitalized patients with AHF, introduces a significant between-trial difference in design

and patient population. However, the HEART-FID study is a substantially larger trial, so any skewing of results due to the more at-risk population in the AFFIRM-AHF study may not be substantial. A sensitivity analysis excluding the AFFIRM-AHF study could have been useful to address this difference in patient population. Despite this minor concern, the treatment effect in the AFFIRM-AHF study was not consistently the highest in magnitude. In fact, the CONFIRM-HF study generally showed the largest treatment effect but also had the widest 95% CIs across all co-primary composite outcomes and their components. Further exploration into this observation may be warranted, but it does not discredit the meta-analysis results. In the publication, between-trial heterogeneity in treatment effect was explored and models were adjusted for baseline hemoglobin and region, which was considered appropriate. The study authors state that there was no identified heterogeneity between the trials for any primary or key secondary outcomes, and that the treatment arms appeared to be balanced by demographics.

Discussion

Summary of Available Evidence

Four double-blind, placebo-controlled RCTs were the primary sources of evidence for the efficacy and safety of FCM in adult patients with HF and ID for improving oxygen capacity. The studies included were the FAIR-HF (N = 459), CONFIRM-HF (N = 304), and HEART-FID (N = 3,065) studies in patients with CHF, and the AFFIRM-AHF study (N = 1,132) in patients with AHF. Of these, 2 studies (FAIR-HF and CONFIRM-HF) were focused primarily on clinical efficacy outcomes such as exercise capacity and NYHA class, while the remaining 2 studies (HEART-FID and AFFIRM-AHF) were focused primarily on composite outcomes related to hospitalizations and deaths. The studies ranged in duration from approximately 6 months (the FAIR-HF study) to 12 months (CONFIRM-HF, HEART-FID, and AFFIRM-AHF studies).

At baseline, mean patient ages were approximately 68 years to 71 years across the treatment groups, the proportion of female patients ranged from 33% to 55%, and the overwhelming majority of patients belonged to NYHA class II or class III, with very few patients belonging to class IV (< 4% in the AFFIRM-AHF study and < 1% in the HEART-FID study) or class I (< 3% in the AFFIRM-AHF study). The 3 CHF studies had a maximum allowed LVEF at screening or index visit, although the precise threshold varied: 40% or less (NYHA class II) or 45% or less (NYHA class III) in the FAIR-HF study, 45% or less in the CONFIRM-HF study, 40% or less in the HEART-FID study (although historically reduced LVEF was also allowed given specific circumstances). In the AFFIRM-AHF study, the inclusion criteria required that patients had an LVEF of less than 50% within 12 months before randomization. All 4 included studies required serum ferritin to be less than 100 mcg/mL, or 100 mcg/mL to 299 mcg/mL or 100 mcg/mL to 300 mcg/mL in combination with a TSAT of less than 20%. White race was disproportionately over-represented in all studies. The percent of patients who identified as white race was 86% in the HEART-FID study, 95% in the AFFIRM-AHF study, and 99% to 100% in the FAIR-HF and CONFIRM-HF studies. Comorbidities were common, including hypertension, dyslipidemia, diabetes, atrial fibrillation, angina pectoris, and others.

There was no direct or indirect evidence submitted that compared FCM to other IV iron products, the most appropriate direct comparator, in patients with HF and ID. No long-term extension studies were submitted. Some additional studies of FCM in the target population are summarized briefly in Appendix 1 as they were not expected to contribute to conclusions of this report.

Interpretation of Results

Efficacy

FCM is a third-generation IV iron formulation with a Health Canada–approved indication for the treatment of ID in adult patients with HF and NYHA class II or class III to improve exercise capacity. The treatment goals of FCM in patients with HF, according to clinical expert and clinician group input, are primarily to improve exercise capacity and alleviate symptoms associated with ID, which can be particularly bothersome and resistant to oral treatments in the HF population. The clinical expert indicated that IV iron is currently the preferred and guideline-recommended[4,25-27] route for treatment of ID in patients with HF, and the intention of iron supplementation for ID in patients with HF is to improve HRQoL, functional capacity, and exercise capacity. Objective outcomes related to hospitalization and mortality were also considered to be of interest given the serious nature of HF.

Findings from 3 RCTs in CHF and 1 RCT in AHF demonstrated potential benefit of FCM compared to placebo in patients with HF and ID based on 24-week and 52-week outcomes. Evidence from 3 CHF studies, considered together, demonstrated that treatment with FCM likely results in an improvement in NYHA class at 24 weeks and 52 weeks, KCCQ at 52 weeks, fatigue score at 24 weeks and 52 weeks, and serum ferritin at 24 weeks and 52 weeks. There is uncertainty regarding whether the magnitude of benefit is clinically meaningful for all of the aforementioned outcomes. Treatment with FCM in patients with CHF may also result in an improvement in KCCQ at 24 weeks but the certainty was lower at this time point due to imprecision. In CHF, the evidence was very uncertain with regards to the effect of FCM on 6MWT at 24 weeks or 52 weeks due to inconsistency, imprecision, and missing data; notably, older studies (FAIR-HF and CONFIRM-HF) showed likely clinically meaningful benefit while a more recent and larger study (HEART-FID) did not show an important benefit, and the reason for this discrepancy is not fully clear. FCM may result in little to no difference in CV mortality when compared to placebo at 26 weeks or 52 weeks, but the duration of follow-up may be inadequate and studies may be inadequately powered to assess this outcome fully.

Evidence from 1 AHF study demonstrated that FCM likely results in an improvement in NYHA class at 24 weeks and 52 weeks, KCCQ at 24 weeks, and serum ferritin at 24 weeks and 52 weeks, CV hospitalization rate at 24 weeks and 52 weeks, and may result in little to no difference in CV mortality at 24 weeks or 52 weeks. There was uncertainty regarding whether the magnitude of effect observed was clinically meaningful for all of the aforementioned outcomes. There were no data available to inform the effect of FCM on 6MWT or fatigue in patients with AHF.

The HEART-FID study was designed primarily to evaluate hospitalizations and deaths, but did report other outcomes of interest such as 6MWT, and interestingly, showed less benefit of FCM than the older studies, which was the source of most inconsistency observed in the GRADE assessment; speculatively, this

could be a function of differences in background therapies, advancements in standard of care, changes in demographics of affected patients over time, differences in imputation of missing data (potential risk of bias in the HEART-FID study as previously discussed), and differences in recruitment countries. However, it is difficult to draw a conclusion on the actual causative factors.

For the outcome of NYHA, the clinical expert consulted by CDA-AMC described that an improvement of 1 class is clinically meaningful in a single patient, but for the purpose of interpreting a between-group OR using the GRADE approach, the null value was used as a threshold for potential harm or benefit. There were some concerns regarding missing data despite imputation approaches in some studies.

The driver of uncertainty in the results for 6MWT was inconsistency between the studies and that CIs and some effect estimates included potential for both clinically meaningful benefit and little to no benefit. The largest study, the HEART-FID study, is also the most recent and enrolled patients the most similar to the population of patients with HF living in Canada with regards to geographical location of the sites; this study also found the least apparent benefit in 6MWT, and its 95% CIs did not or minimally overlapped with those of the other studies contributing data to this outcome. There were also some concerns about missing data.

Results for the change in KCCQ from baseline were very uncertain due to inconsistency between 2 studies and imprecision at 24 weeks, but at 52 weeks, only 1 study informed the evidence. It is unknown whether the magnitude of benefit observed is clinically meaningful. Although some MIDs were provided by the sponsor, these were within-group MIDs, so they were not directly used for GRADE. Fatigue was only evaluated in the CONFIRM-HF study, and there were concerns about missing data which leads to a risk of bias.

Serum ferritin results also had missing data, resulting in lowered certainty in the magnitude of effect, although the direction of effect appeared to be clear and plausible. As ID in HF is defined as serum ferritin less than 100 mcg/mL (absolute ID) or serum ferritin of 100 mcg/mL to 300 mcg/mL with TSAT less than 20%, and the differences between treatment groups were well in excess of a 100 mcg/mL change from baseline, it stands to reason that this is a meaningful benefit, although it does not represent the totality of laboratory workups that would be conducted for a patient with HF and ID. In real-world practice, ferritin would not be evaluated in isolation to evaluate ID, and ultimately the clinical benefits are more important to patients and clinicians. Additionally, there were substantial missing patient data for this outcome.

For both CV hospitalization and CV mortality, there was no available MID, and so the null value was used as a threshold for potential benefit and harms. For CV hospitalization, it was assumed patients who died would contribute to risk of bias due to missing data. For CV mortality there were no particular concerns regarding missing data. The clinical expert consulted by CDA-AMC highlighted that the duration of the trials (6 months to 12 months) is likely insufficient to elucidate a difference for mortality. Additionally, the studies were not powered to detect changes in mortality alone, as the studies which did investigate this as a primary end point and created composite outcomes including mortality instead. Notably, the clinical expert consulted by CDA-AMC also underscored that hospitalization and mortality rate are not the key treatment outcomes of iron supplementation in the context of HF and ID, as iron supplementation is not a disease-modifying treatment for the underlying HF which drives these outcomes much more directly than does ID itself. It is clinically reasonable to suspect there may be some degree of benefit on a grander timescale for these outcomes

because untreated ID is a poor prognostic factor for HF, but the primary goal of iron supplementation for the relief of ID is to replenish and maintain iron stores for the purpose of improving symptoms such as fatigue and improving exercise capacity. Life-prolonging treatments would likely be those that are disease-modifying for HF directly, rather than ID.

The HEART-FID study's primary outcome (which was a hierarchical composite that included death at 12 months, hospitalizations for HF at 12 months, and change in 6MWT at 6 months) did not reach statistical significance in the comparison between FCM and placebo. Results of prespecified sensitivity and supportive analyses were consistent with the primary results. In particular, the authors of this study highlighted a lack of reduction in long-term hospitalizations for HF in the trial, noted that the patients may be lower risk than those enrolled in studies of AHF, and underlined a relatively high use of other evidence-based medications (e.g., sacubitril-valsartan) in the HEART-FID study. Though not possible to objectively determine, with the HEART-FID study being both the only study conducted in North American sites and the most recent of all the included studies in this review, inconsistency between the outcomes of the HEART-FID study (e.g., 6MWT) and analogous outcomes of the other studies may be in part due to differences in the background management of patients over time and across geographical barriers.

There are some considerations for the external generalizability of these studies. The studies disproportionately enrolled patients of white race, especially the FAIR-HF (> 99%), CONFIRM-HF (86%), and AFFIRM-AHF (95%) studies, even for the regions in which they were conducted, but especially when applying the results of these studies to the diversity of the patient population living in Canada. The geography of the study sites may also be considered. The FAIR-HF study was conducted in Europe, but the majority of study sites and majority of patients were located in Russia (43.8%), Ukraine (21.4%), and Poland (14.1%), followed by Spain (4.3%) and Romania (3.3%), while the CONFIRM-HF study was conducted exclusively in Poland and Russia. Sites included in the AFFIRM-AHF study included Argentina, Brazil, Israel, and Eurasia (Croatia, Georgia, Italy, Lebanon, the Netherlands, Poland, Romania, Singapore, Spain, Sweden, Ukraine, and the UK). The health care systems of these countries and the prevalence, quality, and type of optimal background therapy may differ from Canada. In contrast, study sites in the HEART-FID study were located primarily in the US, but also included sites in Canada in several provinces, Europe (Czechia, Hungary, Georgia, Latvia, Lithuania, Poland, Russia, and Ukraine), New Zealand, and Australia; while there are likely geographical differences in treatment practices and patient populations, the inclusion of North American sites may signal more generalizability of the HEART-FID study's patient population compared to the other studies, when considering the Canadian health care context.

The requested reimbursement criteria specify a NYHA class of II to class III inclusive, which reflects the eligibility criteria of the FAIR-HF and CONFIRM-HF studies. The clinical expert consulted by CDA-AMC highlighted that the clinical practice guidelines for HF from Canada,[4] Europe,[26,27] and the US[25] do not differentiate by NYHA class in their recommendations for the management of ID. Treatment recommendations for ID in the context of HF are differentiated only by laboratory markers such as serum ferritin, TSAT, and hemoglobin levels, and patients with diagnosed ID in the context of HF should likely be receiving IV iron supplementation according to the guidelines. In addition to class II and class III, the HEART-FID study included patients with class IV and the AFFIRM-AHF study included patients with any NYHA class

(i.e., class I to class IV inclusive). Few of the included patients (i.e., < 3% in each study) were outside of the target population according to the reimbursement criteria, but this may be an area of scope creep in actual clinical practice as reflected by the Canadian treatment guidelines. According to clinical expert input, patients in NYHA class I or class IV are not expected to have differences with regards to their response to FCM for iron repletion compared to patients in NYHA class II or class III. However, very limited data are available to confirm that the treatment effect in NYHA class I or class IV would be similar to what was observed in the trials.

Interestingly, the HF guidelines in different regions also differ with regards to whether specific IV iron formulations are recommended. The 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure does not specify a particular IV iron formulation, nor do the US guidelines. In contrast, the European Society of Cardiology HF guidelines recommend treatment with IV FCM or ferric derisomaltose, specifically. The reasons why these 2 formulations were specifically recommended are not described explicitly, but based on the evidence presented in the guidelines, it can be inferred that it is because there are clinical trials in the HF population for both of these formulations.

Most critically, the only evidence submitted for the patient population of HF and ID was compared to placebo, with no active comparator. No direct or indirect evidence comparing FCM to other IV iron preparations is known to exist. This represents a substantial gap in the evidence, as clinical practice guidelines and indeed, common clinical practice in Canada, rely primarily on IV formulations of iron to treat ID in populations with HF. Patients with HF have altered physiology as a result of their heart disease that precludes effective absorption of oral iron, and there is a demonstrated insufficient efficacy of oral supplementation in this population,[47] even beyond the general population issues of low absorption, GI side effects, and low compliance. It is therefore impossible to draw a conclusion on the efficacy or safety of FCM compared to other treatments typically used in clinical practice in these populations. The intended benefit of FCM, as stated by the sponsor, is a shorter infusion time than comparators; this is evident from the administration guidelines provided in the product monographs for FCM versus the comparators, albeit no direct data regarding average or minimum/maximum infusion times were provided to support this.

Results from the meta-analysis by Ponikowski and colleagues[33] which utilized individual patient data from the CONFIRM-HF, HEART-FID, and AFFIRM-AHF studies appeared to be clinically important, demonstrating that compared to placebo, patients treated with FCM experienced reduction in the composite outcome of total CV hospitalization and CV death, total hospitalizations, and total HF hospitalizations. However, it was noted that the meta-analysis did not show a reduction in time to CV death or time to all-cause death, nor did it report on HRQoL outcomes or exercise capacity (e.g., 6MWT). It is also worth noting that the meta-analysis by Ponikowski and colleagues[33] explored the outcomes related to baseline TSAT and it was reported that those with a TSAT less than 15% was the only group that resulted in reduction in the composite outcome of total CV hospitalizations and CV death while those with baseline TSAT between 15% and 24% and TSAT of at least 24% did not appear to derive statistically significant benefit from FCM therapy. The same trends were observed for the composite outcome of total HF hospitalization and CV death.

A concurrent review of FCM in IDA (without HF) is under way; in this review, a published indirect treatment comparison was appraised,[68] which compared FCM with ferric derisomaltose and iron sucrose in patients with IDA and inflammatory bowel disease. Briefly, point estimates for the ORs assessing hemoglobin response comparing FCM with ferric derisomaltose and iron sucrose favoured FCM; however, the 95% credible intervals were wide and included effects favouring the comparator interventions. Harms were not assessed in the network meta-analysis, and important efficacy outcomes relevant to patients with HF and ID were also not assessed. Therefore, the summary of the published network meta-analysis submitted by the sponsor was insufficient to determine whether there is a difference in efficacy or harms for FCM compared to other injectable forms of iron in patients with IDA and inflammatory bowel disease.

Treatment practice related to ID in the context of HF, according to the clinical expert consulted by CDA-AMC and in following the treatment guidelines, is focused on patients with reduced ejection fraction. Patients with HF and preserved ejection fraction are not considered in this review, and the included studies all required reduced ejection fraction as a component of their patient eligibility criteria.

Harms

FCM was well tolerated in all of the included studies. The frequency of AEs was generally similar between treatment groups within each included study, where reported, although some AEs (e.g., administration site conditions, GI disorders) appeared to be more common in the FCM groups. These trends align with the expected pathophysiology of HF and ID and the expected treatment effect and side effects of iron supplementation. There were slightly more patients who experienced SAEs in the placebo groups than the FCM groups, and these were most commonly cardiac disorders.

FCM is associated with a risk of hypophosphatemia, as detailed in the product monograph, which is not the case to the same magnitude among the other IV iron formulations. Events of hypophosphatemia were rare in the included studies, where reported, but there are concerns about the reporting given that events (including several severe events) do appear to have occurred without being recorded as TEAEs in the CONFIRM-HF study. It is unknown whether similar events occurred in the other trials and were unreported. Discussion with clinical experts consulted in the FCM review pertaining to patients with IDA (outside of the HF context) elucidated that hypophosphatemia is relatively easy to manage with inexpensive oral supplements, although it may incur additional monitoring costs, and untreated hypophosphatemia can result in serious health risks. The sponsor was requested to provide data on how frequently these laboratory events were observed across all studies but declined; however, further clarification was provided that the reason such laboratory events were not reported as TEAEs is because an isolated laboratory finding of hypophosphatemia without clinical symptoms was not considered by investigators as an AE. The sponsor also described in their response that laboratory-assessed hypophosphatemia is less common in patients with HF than in other therapeutic areas and referenced a study by Rosano and colleagues[69] in a pooled analysis of individual patient data from 41 studies including 7,931 adults with ID across disease states and therapeutic areas, in which the authors also noted that clinical events associated with hypophosphatemia were uncommon with FCM therapy in the HF population. Speculatively, the sponsor noted that this event may be less common in patients with HF than other therapeutic areas due to concomitant decreases in kidney function being common in patients

with HF. However, there is a lack of direct evidence to support this, and it is unknown whether there could be widespread reporting issues regarding hypophosphatemia in studies of IV iron therapies in patients with HF and ID.

Conclusion

Findings from 3 RCTs in CHF and 1 RCT in AHF demonstrated potential benefit of FCM compared to placebo in patients with HF and ID based on 24-week and 52-week outcomes. Evidence from 3 CHF studies, considered together, demonstrated that treatment with FCM likely results in an improvement in NYHA class at 24 weeks and 52 weeks, KCCQ at 52 weeks, fatigue score at 24 weeks and 52 weeks, and serum ferritin at 24 weeks and 52 weeks. There is uncertainty regarding whether the magnitude of benefit is clinically meaningful for all of the aforementioned outcomes. Treatment with FCM in patients with CHF may also result in an improvement in KCCQ at 24 weeks but the certainty was lower at this time point due to imprecision. In CHF, the evidence was very uncertain with regards to the effect of FCM on 6MWT at 24 weeks or 52 weeks due to inconsistency, imprecision, and missing data; notably, older studies (FAIR-HF and CONFIRM-HF) showed likely clinically meaningful benefit while a more recent and larger study (HEART-FID) did not show an important benefit, and the reason for this discrepancy is not fully clear. FCM may result in little to no difference in CV mortality when compared to placebo at 26 weeks or 52 weeks, but the duration of follow-up may be inadequate and studies may be inadequately powered to assess this outcome fully.

Evidence from 1 AHF study demonstrated that FCM likely results in an improvement in NYHA class at 24 weeks and 52 weeks, KCCQ at 24 weeks, and serum ferritin at 24 weeks and 52 weeks, CV hospitalization rate at 24 weeks and 52 weeks, and may result in little to no difference in CV mortality at 24 weeks or 52 weeks. There was uncertainty regarding whether the magnitude of effect observed was clinically meaningful for all of the aforementioned outcomes. There were no data available to inform the effect of FCM on 6MWT or fatigue in patients with AHF.

FCM was well tolerated in all included studies. The frequency of AEs was generally similar between treatment groups within each included study, where reported. These trends align with the expected pathophysiology of HF and ID and the expected treatment effect and side effects of iron supplementation. There were slightly more patients who experienced SAEs in the placebo groups than the FCM groups, and these were most commonly cardiac disorders. FCM is associated with a risk of hypophosphatemia, as detailed in the product monograph, and these events appeared relatively uncommon in the included studies in all treatment groups.

Other IV formulations of iron supplementation exist and are used in clinical practice to treat patients with HF and ID, albeit without a specific indication for this population. There is a lack of direct or indirect evidence comparing FCM to other second-generation or third-generation IV iron formulations, which represent the direct comparators of FCM. According to clinical practice guidelines in Canada and around the world, as well as clinical expert input, IV iron is standard of care for patients with HF and ID to improve exercise capacity and symptoms. The treatment goal of IV iron is not necessarily to improve hospitalization and mortality

directly as these are likely more strongly driven by the patient's underlying HF, which is not modified by iron supplementation. Although FCM was demonstrated to be reasonably effective and safe compared to placebo, no conclusions can be drawn regarding the relative efficacy and safety of FCM with other commonly used IV iron formulations such as iron sucrose or ferric derisomaltose in the HF population.

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Appendix 1: Additional Studies

Please note that this appendix has not been copy-edited.

Table 27: Summary of Studies in HF and ID That Were Excluded From the Review

Study name or number	Clinical trials registry number	Geography	Phase	N	Study design	Population	Notes on why it was excluded
Caravita et al. (2022)[70]	EUCTR2012 to 005830 to 12 (data not reported)	Italy	NR	70	DB MC PC RCT FCM 500 mg every 3 weeks vs. PBO	HF and IDA	Small sample size, geography, no identified gaps in review addressed by design or outcomes in this study
IRON-CRT Martens et al. (2021)[71]	NR	Belgium	NR	75	DB PC MC RCT FCM vs. SOC plus PBO	HF and ID	Small sample size, geography, no identified gaps in review addressed by design or outcomes in this study
Myocardial-IRON Nunez et al. (2020)[72]	NCT03398681 (data not reported) EUCTR2016 to 004194 to 40 (data not reported)	Spain	4	53	DB PC MC RCT FCM 1,000 mg vs. PBO	HF and IDA	Small sample size, geography, no identified gaps in review addressed by design or outcomes in this study
FER-CARS-01 (no reference provided)[73]	NR	Russia	3	NR	DB PC AC MC RCT	ID, congestive HF, renal failure	12-week study, sample size NR, geography, no identified gaps in review addressed by design or outcomes in this study
EFFECT-HF FER-CARS-04 van Veldheisun et al. (2017)[74]	NCT01394562	The Netherlands	3b	174	OL SC RCT FCM vs. SOC which could include oral iron at physician discretion	HF and ID	Comparator arm allowed for but did not require use of oral iron supplements based on clinician decision (29 of 86 patients in the SOC group were receiving oral iron), complicating interpretation in the context of this review (Note: also excluded by sponsor SLR for the same reason)

AC = active-controlled; CO = crossover; DB = double blind; HF = heart failure; ID = iron deficiency; IDA = iron deficiency anemia; MC = multicentre; OL = open label; PC = placebo controlled; RCT = randomized controlled trial; SLR = systematic literature review; SOC = standard of care.

Source: Information in the table was taken from the sponsor's submitted Summary of Clinical Evidence.

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Abbreviations

BIA	budget impact analysis
CDA-AMC	Canada's Drug Agency
CKD	chronic kidney disease
HF	heart failure
ID	iron deficiency
IDA	iron deficiency anemia
NYHA	New York Heart Association

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Ferric carboxymaltose (Ferinject), 50 mg/mL elemental iron/mL, vial for injection (2 mL, 10 mL, 20 mL)
Indication	For the treatment of ID in adult patients with HF and NYHA class II/III to improve exercise capacity. The diagnosis of ID must be based on laboratory tests.
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	March 11, 2024
Reimbursement request	As per indication
Sponsor	CSL Vifor
Submission history	Previously reviewed: No

HF = heart failure; ID = iron deficiency; NOC = Notice of Compliance; NYHA = New York Heart Association.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	Adult patients with HF and NYHA class II or class III to improve exercise capacity.
Treatment	Ferric carboxymaltose
Dose regimen	The sponsor estimated an average cumulative iron dose (i.e., a treatment course) of 1,500 mg per patient (weight-based and dependent on hemoglobin levels). A single ferric carboxymaltose administration should not exceed either 15 mg iron/kg of body weight or 1,000 mg of iron. If the total iron need (i.e., cumulative iron dose) is higher, then the administration of an additional dose should be a minimum of 7 days apart from the first dose.
Submitted price	Ferric carboxymaltose, 50 mg elemental iron per mL, IV • $45.00 per 2 mL single-use vial • $225.00 per 10 mL single-use vial • $450.00 per 20 mL single-use vial
Submitted treatment cost	$800 per treatment course
Comparator	• Ferric derisomaltose • Iron sucrose
Perspective	Canadian publicly funded health care payer
Time horizon	Single treatment course (i.e., 1 cumulative iron dose)
Key data source	No direct or indirect evidence was provided by the sponsor for the indicated population comparing ferric carboxymaltose to iron sucrose and ferric derisomaltose. The FERGIcor and REPAIR-IDA open-label, randomized controlled trials comparing ferric carboxymaltose to iron sucrose in patients with IBD and CKD; a 2017 published meta-analysis

Component	Description
	(comparing ferric carboxymaltose to iron sucrose, ferric derisomaltose, and oral iron in patients with irritable bowel disease); and 2 indirect treatment comparisons (Pollock and Muduma and Han and colleagues) in several other indications.
Costs considered	Drug acquisition costs, administration costs
Submitted results	Ferric carboxymaltose was associated with cost savings compared to ferric derisomaltose and iron sucrose (incremental savings of $15 and $394, respectively, per patient, per treatment course).
Key limitations	• The sponsor assumed equivalent efficacy and safety between ferric carboxymaltose and comparators is uncertain. The CDA-AMC clinical review report found that there is a lack of direct or indirect evidence comparing ferric carboxymaltose to other IV iron formulations for the treatment of ID in patients with HF. No conclusions can be drawn regarding the relative efficacy and safety of ferric carboxymaltose for this indication. Ferric carboxymaltose is associated with a risk of hypophosphatemia, as detailed in the product monograph, with implications for monitoring and treatment costs. If hypophosphatemia is of clinical importance, a cost-utility analysis should have been submitted. Furthermore, the costs of managing adverse events, specifically treatment-emergent hypophosphatemia, were not included in the sponsor's analysis. • Clinical expert feedback obtained by CDA-AMC noted that iron sucrose is not among the recommended treatments in the clinical practice guidelines published by the European Society of Cardiology1 (only ferric derisomaltose and ferric carboxymaltose) for this patient population. Therefore, iron sucrose is unlikely to be a relevant comparator in this indication and the expected cost savings estimated from the comparison with iron sucrose is uncertain. • Variability exists in clinical practice on the approach to calculate total iron dose per treatment course that would impact the expected cost savings derived from administration costs (nursing time, infusion chair time, and infusion devices consumed).
CDA-AMC reanalysis results	CDA-AMC did not undertake a base-case reanalysis. Given the higher rates of hypophosphatemia observed with ferric carboxymaltose, the extent of savings that will be realized with the use of ferric carboxymaltose compared to iron sucrose or ferric derisomaltose is highly uncertain. A scenario analysis including costs associated with monitoring and treating patients with nonsevere hypophosphatemia estimated that cost savings would be reduced. Reimbursement of ferric carboxymaltose may lead to additional costs to the health care system that may not have been fully considered within this analysis.

CDA-AMC = Canada's Drug Agency; CKD = chronic kidney disease; HF = heart failure; IBD = inflammatory bowel disease; ID = iron deficiency; NYHA = New York Heart Association.

Conclusions

The clinical review by Canada's Drug Agency (CDA-AMC) concluded that ferric carboxymaltose demonstrated potential benefit when compared to placebo in patients with heart failure (HF) and iron deficiency (ID) in terms of an improvement in New York Heart Association (NYHA) class, higher serum ferritin levels, and reduced hospitalization. However, there was a lack of direct and indirect evidence comparing ferric carboxymaltose to other IV iron formulations in the HF population. Particularly, the assumption of equivalent safety remains highly uncertain and may be inappropriate as ferric carboxymaltose is associated with a risk of hypophosphatemia that may require additional monitoring and treatment, as detailed in the product monograph,[2] which is not the case to the same magnitude among the other IV iron formulations. If hypophosphatemia has a nonnegligible quality of life impact in patients with HF, a cost-utility analysis would have been the preferred approach for the pharmacoeconomic analysis.

The sponsor submitted a cost-minimization analysis assuming equivalent clinical efficacy and safety between ferric carboxymaltose, iron sucrose, and ferric derisomaltose. In the submission, ferric carboxymaltose was associated with cost savings of $15 and $394 per patient per treatment course when compared to ferric derisomaltose and iron sucrose, respectively, at public list price. However, the costs of monitoring and treating hypophosphatemia were not included by the sponsor. CDA-AMC did not undertake a base-case reanalysis as the limitations identified by CDA-AMC could not be addressed given that they were related to the underlying assumption of equivalent clinical efficacy and safety between ferric carboxymaltose and its comparators, and the variability of the administration of the total iron dose per treatment course. A scenario analysis was conducted that included monitoring and treatment costs based on assumptions and expert opinion for nonsevere hypophosphatemia. This analysis estimated that cost savings would be reduced (incremental savings = $3 compared to ferric derisomaltose and $382 compared to iron sucrose); however, if rates of hypophosphatemia requiring treatment and monitoring are higher than assumed (10% based on CDA-AMC clinical expert opinion) or if patients develop more severe adverse events (e.g., severe hypophosphatemia, hypophosphatemic osteomalacia, and/or fractures), savings associated with the reimbursement of ferric carboxymaltose may be further reduced or eliminated. Due to the remaining uncertainty concerning the comparative safety across iron products and its associated costs, the magnitude of cost savings associated with ferric carboxymaltose remains uncertain. All costs and incremental savings are further based on publicly available list prices and may not reflect actual prices paid by Canadian public drug plans.

Economic Review

The current review is for ferric carboxymaltose (Ferinject) for the treatment of ID in adult patients with HF and NYHA class II or class III to improve exercise capacity.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-minimization analysis for ferric carboxymaltose compared with ferric derisomaltose and iron sucrose for the treatment of ID in adult patients with HF and NYHA class II or class III to improve exercise capacity. The reimbursement population aligns with the Health Canada–indicated population.

The sponsor assumed ferric carboxymaltose was associated with equivalent clinical efficacy and safety to ferric derisomaltose and iron sucrose, based on the following published literature: randomized controlled trials comparing ferric carboxymaltose with iron sucrose in patients with inflammatory bowel disease (FERGIcor study)[3] and chronic kidney disease (CKD) (REPAIR-IDA study);[4] a 2017 published meta-analysis assessing the efficacy and tolerability of iron supplements in patients with inflammatory bowel disease (ferric carboxymaltose, iron sucrose, ferric derisomaltose, and oral iron);[5] an indirect treatment comparison

by Pollock and Muduma comparing either ferric carboxymaltose or ferric derisomaltose to iron sucrose in patients with inflammatory bowel disease, nondialysis-dependent CKD, or heavy uterine bleeding;[6] and an indirect treatment comparison by Han and colleagues in patients with inflammatory bowel disease, heavy uterine bleeding, ID anemia (IDA)–related pregnancy, or patients with IDA.[7] The analysis was conducted from the perspective of the publicly funded health payer over a time horizon corresponding with treatment duration (i.e., 1 treatment course). As a treatment course is less than 1 year, discounting was not applied.

Ferric carboxymaltose is available as a single-use vial, administered intravenously by infusion (diluted) or injection (undiluted). The recommended dosage of ferric carboxymaltose is dependent on hemoglobin level and the weight of each patient, and can range from 500 mg to 2,000 mg. The sponsor assumed a mean hemoglobin level of 10.22 g/dL, derived from the average pretreatment hemoglobin level for patients with IDA treated with IV iron in 1 Alberta hospital,[8] and a mean weight of 76.0 kg based on the demographics of patients with IDA in published literature.[9] As a result, an average cumulative iron dose of 1,500 mg per patient was assumed. At the submitted price of $45 per 100 mg vial, the sponsor estimated the drug costs associated with ferric carboxymaltose per treatment course to be $675 per patient. At the same cumulative iron doses, the drug cost per treatment course of ferric derisomaltose was the same as ferric carboxymaltose ($675); and was $413 per patient per treatment course of iron sucrose.

The sponsor also included costs related to treatment administration which comprise time with the nurse, infusion chair time, and infusion devices consumed. These costs are influenced by 3 main factors: the approach used to calculate the cumulative iron dose corresponding to the total iron need, the maximum iron dose per single infusion of each drug, and the minimum infusion time of each drug. To calculate the cumulative iron dose, the sponsor used the simplified tables from the ferric carboxymaltose product monograph for all treatment arms in the model. To calculate the maximum iron dose per single infusion, the sponsor assumed that a single infusion should not exceed: either 15 mg/kg or 1,000 mg for ferric carboxymaltose, 20 mg/kg or 1,500 mg for ferric derisomaltose (informed by their respective product monographs[2,10]), and 300 mg for iron sucrose (to align with the CDA-AMC review of Monoferric).[11] The minimum infusion time adopted by the sponsor was based on the respective product monographs: 6 minutes to 15 minutes for ferric carboxymaltose, 20 minutes to 30 minutes for ferric derisomaltose, and 90 minutes for iron sucrose. The IV preparation time per infusion and monitoring time postinfusion were assumed to be identical for all iron products (6 minutes and 30 minutes, respectively). The sponsor assumed 100% adherence and no vial sharing. When including administration costs, a treatment course with ferric carboxymaltose was estimated by the sponsor to be $800 per patient.

Base-Case Results

The sponsor presented both probabilistic (based on 5,000 iterations) and deterministic results. While deterministic and probabilistic results were similar when ferric carboxymaltose was compared to iron sucrose, when compared to ferric derisomaltose the results did not align (i.e., ferric carboxymaltose was cost saving in the probabilistic analysis and more costly in the deterministic analysis). This was because, across each probabilistic run, changes to the mean patient weight and hemoglobin levels resulted in more variability

in the number of infusions needed to deliver ferric derisomaltose as it has a higher threshold for maximum iron dose per single infusion.

The sponsor's submitted base case estimated a total cost per treatment course with ferric carboxymaltose of $852 per patient; while the total cost per treatment course with ferric derisomaltose and iron sucrose was estimated to be $867 and $1,246 per patient, respectively (Table 3). Based on the sponsor's results, treatment with ferric carboxymaltose resulted in estimated cost savings of $15 and $394 per patient per treatment course compared with ferric derisomaltose and iron sucrose, respectively. Drug acquisition costs accounted for the majority of total costs for ferric carboxymaltose ($725 [85%]).

The cost savings estimated by the sponsor were entirely driven by reduced administration costs (nurse time, infusion chair time, and infusion devices consumed) as ferric carboxymaltose had the same drug acquisition costs as ferric derisomaltose (incremental drug cost = $0) and higher drug acquisition costs (incremental drug cost = $282) compared with iron sucrose.

Table 3: Summary of the Sponsor's Economic Evaluation Results and Scenario Analysis

Scenarios	Drug	Total drug costs ($)	Incremental drug costs ($)	Total costs ($)	Incremental costs ($)
Sponsor's base case Using a total iron dose of 1,500 mg across all comparators (FCM PM simplified tables)	FCM	725	Reference	852	Reference
	FD	725	—	867	−15
	IS	443	282	1,246	−394
Scenario 1: Using a fixed total iron dose of 1,000 mg across all comparators (capped by IS PM dosing)	FCM	450	Reference	526	Reference
	FD	450	—	574	−48
	IS	275	175	853	−327
Scenario 2: Using the recommended approach per each respective PM	FCM	732	Reference	849	Reference
	FD	732	—	873	−24
	IS	275	448	852	−3

FCM = ferric carboxymaltose; FD = ferric derisomaltose; IS = iron sucrose; PM = product monograph.

Note: A negative sign refers to cost savings.

Source: Sponsor's pharmacoeconomic submission based on the results from the re-submitted model file (as the results in the submitted pharmacoeconomic report were not updated accordingly).[12]

Sensitivity and Scenario Analysis Results

The sponsor conducted several scenario analyses to explore the impact on costs of alternative assumptions to calculate the total iron dose (i.e., a treatment course) based on different methods (i.e., Ganzoni formula, simplified tables from the ferric derisomaltose product monograph, a fixed-dose approach [1,000 mg], cumulative iron based on the respective product monographs) and alternative assumptions for the maximum dose per single infusion (1,000 mg for ferric carboxymaltose and ferric derisomaltose, and 300 mg for iron sucrose as per the Monoferric CDA-AMC Pharmacoeconomic Review Report reanalysis[11]). Treatment with ferric carboxymaltose was still less costly than both comparators across all scenarios (selected scenarios are presented in Table 3). These were entirely driven by reduced administration costs. However, the magnitude

of the cost savings differed by more than 15% in half the comparisons, highlighting the uncertainty in the cost savings which are dependent on how total iron doses are calculated and the number of infusions required in clinical practice.

The sponsor additionally considered a scenario exploring the impact of adopting a societal perspective, which included additional costs associated with patient lost income, estimated based on time missed at work to travel and receive IV infusions, employment rate, and hourly wage. The cost savings associated with ferric carboxymaltose treatment were reduced when compared with ferric derisomaltose but increased when compared with iron sucrose.

CDA-AMC Appraisal of the Sponsor's Economic Evaluation

CDA-AMC identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis.

- **The assumption of equivalent clinical efficacy and safety between ferric carboxymaltose and its comparators is uncertain:** The sponsor assumed equivalent efficacy and safety between ferric carboxymaltose and other IV iron therapies, ferric derisomaltose and iron sucrose, based on selected studies.[3-7] However, the populations included in these studies do not align with the patient population of interest for this reimbursement request. The CDA-AMC clinical review found that there is a lack of direct or indirect evidence comparing ferric carboxymaltose to other IV iron formulations for the treatment of ID in patients with HF. As a result, no conclusions can be drawn regarding the relative efficacy and safety of ferric carboxymaltose and other commonly used IV formulations for this indication.

  The sponsor's assumption of equivalent safety remains highly uncertain. Of particular concern is the increased risk of hypophosphatemia associated with ferric carboxymaltose, as noted in its product monograph,[2] which is not the case to the same magnitude among the other IV iron formulations. Specifically, the product monograph notes the increased risk of hypophosphatemia and hypophosphatemic osteomalacia and fractures (reported in the postmarketing period) that have required surgery.[2] CDA-AMC requested additional information from the sponsor,[13,14] who justified that the clinical importance of increased incidence of hypophosphatemia with ferric carboxymaltose has not been established. The sponsor highlighted that most episodes of hypophosphatemia are biochemically moderate, asymptomatic, and resolve without intervention. The sponsor also described in their response that laboratory-assessed hypophosphatemia is less common in patients with HF than in other therapeutic areas. Where reported, events of hypophosphatemia were rare in the included studies (e.g., the CONFIRM-HF study reported 13 [8.7%] patients in the ferric carboxymaltose treatment group were diagnosed with hypophosphatemia, compared to 1 [0.7%] in the placebo group). However, there are concerns about the reporting given that events (including several severe events) do appear to have occurred without being recorded as treatment-emergent adverse effects in the CONFIRM-HF study. It is unknown whether there could be widespread reporting issues regarding hypophosphatemia in studies of IV iron therapies in patients with HF and ID.

Monitoring for hypophosphatemic osteomalacia is recommended for patients who receive multiple doses of ferric carboxymaltose for long-term treatment and who have any of the following underlying risk factors: vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, hereditary hemorrhagic telangiectasia, inflammatory bowel disease, or osteoporosis.[2] It is recommended that serum phosphate levels be checked in patients at risk of low serum phosphate who require a repeat course of treatment within 3 months. This is aligned with clinical expert input obtained by CDA-AMC and supported by literature.[15,16] While there is no standard of care for managing treatment-emergent hypophosphatemia in patients with HF, patients presenting with this adverse event will likely receive testing to confirm the diagnosis and, potentially, treatment. However, the cost-minimization analysis did not include costs related to monitoring or treating hypophosphatemia after treatment with ferric carboxymaltose. As a result, the validity of the sponsor's cost-minimization analysis is uncertain, and it is uncertain if the estimated cost savings would be realized.

- CDA-AMC was unable to address the lack of comparative clinical evidence in reanalysis.
- CDA-AMC included a scenario analysis with the addition of monitoring and treatment costs for hypophosphatemia. This scenario assumed 10% of patients on ferric carboxymaltose (i.e., 10%) would require testing and treatment based on clinical expert input obtained by CDA-AMC. This would entail 2 laboratory tests, 1 general consultation visit, and the cost of 1 bottle of K-Phos (potassium phosphate and sodium acid phosphate) tablets, reflecting the management expected for nonsevere hypophosphatemia. No costs were applied to the routine management of hypophosphatemia for the comparators as clinical expert input and guidelines[15,16] noted hypophosphatemia is more often a concern associated with the treatment with ferric carboxymaltose.

Additional limitations are identified in the following but were not addressed by CDA-AMC as the limitation pertaining to the lack of comparative clinical evidence could not be addressed.

- **Use of iron sucrose as a treatment for ID in adult patients with HF is uncertain:** The sponsor assumed iron sucrose would be used as an off-label treatment to improve exercise capacity due to ID in adult patients with HF and NYHA class II or class III, in both the inpatient and outpatient setting. In fact, within the sponsor's submitted base case, the largest cost savings associated with the use of ferric carboxymaltose would be from the comparison with iron sucrose. However, clinical expert input obtained by CDA-AMC noted the limited use of iron sucrose in clinical practice to improve exercise capacity due to ID. Iron sucrose is only indicated for patients with CKD to treat IDA, and only half of all patients with HF also have CKD. Also, iron sucrose would not likely be the treatment of choice in clinical practice given the most recent treatment guidelines in this area.[1,17] In the most recent guidelines published by the European Society of Cardiology,[1] ferric carboxymaltose and ferric derisomaltose were the recommended treatment option. Combined with the lack of comparative evidence, the relevance of iron sucrose as a comparator for this indication is uncertain and the estimated cost savings may not be realized.

- **Variability in clinical practice on the total iron dose per treatment course and other infusion planning aspects:** In the sponsor's base case, the approach taken to determine the cumulative iron dose per treatment course (i.e., total iron need) with ferric carboxymaltose, ferric derisomaltose, or iron sucrose was based on the simplified tables from the ferric carboxymaltose product monograph. According to the clinical input obtained by CDA-AMC for this review, there is variability in clinical practice on how the cumulative iron dose to treat patients with IDA is determined. In the context of patients with HF, clinicians most likely will refer to the specific product monograph of each iron product to determine individual patient dosing. This approach results in a different total iron dose per treatment course across comparators and implies that patients treated with different iron products require different cumulative iron doses to address the same needs. However, evidence to support the clinical equivalence of different cumulative iron doses across comparators in patients with ID and HF is lacking. Altogether, these elements of dosing calculation and infusion planning will impact the costs related to nurse time, chair time, and infusion devices consumed. Therefore, the estimated cost savings remain uncertain.
- **Confidential pricing agreements:** The sponsor's analyses use pricing available for the comparator IV iron products from the Ontario Drug Benefit Formulary.[18] However, confidential pricing agreements exist for ferric derisomaltose to treat IDA.[19] Therefore, the submitted price of ferric carboxymaltose may require a price reduction to avoid incurring additional costs relative to ferric derisomaltose.
  - CDA-AMC was unable to address this limitation in reanalysis, as the negotiated prices of other IV iron products are unknown.

CDA-AMC Reanalyses of the Economic Evaluation

Base-Case Results

CDA-AMC did not undertake a reanalysis of the sponsor's submission and presented the sponsor's submitted base case and some selected scenario analyses (Table 3). The limitations identified by CDA-AMC could not be addressed and were related to the underlying assumption of equivalent clinical efficacy and safety between ferric carboxymaltose and comparators, and the lack of good supporting data to assert the costs of monitoring and treating hypophosphatemia.

Under an assumption of equivalent clinical efficacy and safety, treatment with ferric carboxymaltose remains the least costly option, although the magnitude of the cost savings varies depending on the approach used to calculate the total iron dose per treatment course, which in turn impacts savings with infusion time.

A scenario analysis that explored the potential costs associated with monitoring and treating patients with nonsevere hypophosphatemia estimated lowered cost savings associated with ferric derisomaltose (Table 5). This scenario remains highly uncertain. If more than 10% of patients on ferric carboxymaltose require monitoring and treatment, or if patients develop severe hypophosphatemia, hypophosphatemic osteomalacia, and/or fractures, the cost savings associated with ferric carboxymaltose may not be realized.

Issues for Consideration

- Ferric carboxymaltose is currently being reviewed by CDA-AMC for another distinct indication, the treatment of IDA in adult and pediatric patients aged 1 year and older when oral iron preparations are not tolerated or are ineffective.[20]
- Ferric carboxymaltose may be given as an IV bolus in which case the cost associated with infusion time would be reduced. The cost difference between ferric carboxymaltose IV bolus and other IV iron product infusions was not evaluated within this submission.
- For IV iron products, treatment must be administered within a specific time frame after the product has been prepared for infusion (or it would otherwise be wasted) and patients need monitoring after treatment administration.
- While the use of ferric carboxymaltose may be associated with overall cost savings compared to other IV iron products from a Canadian publicly funded health care payer perspective (due to decreased infusion time and thus reduced administration costs), ferric carboxymaltose is associated with higher drug acquisition costs than iron sucrose and similar drug acquisition costs to ferric derisomaltose. Transitioning from these other IV iron products to ferric carboxymaltose may therefore be complicated by increased costs for some budget holders (i.e., public drug plans) while the associated cost savings with administration costs are seen by others (e.g., hospital budget holders). Drug plans noted that there may be a potential for increased patient access within the existing system capacity given the shorter infusion time associated with ferric carboxymaltose and that predicted savings from drug administration may not be realized. When considering drug costs alone, at the publicly available prices, the cost of ferric carboxymaltose is the same as of ferric derisomaltose and it would need to be reduced by 39% to equal that of iron sucrose when considering equivalent cumulative iron doses per treatment course.

Overall Conclusions

The CDA-AMC clinical review concluded that ferric carboxymaltose demonstrated potential benefit when compared to placebo in patients with HF and ID in terms of an improvement in NYHA class, higher serum ferritin levels, and reduced hospitalization. The frequency of adverse events was generally similar between ferric carboxymaltose and placebo, where reported. However, there was a lack of direct and indirect evidence comparing ferric carboxymaltose to other IV iron formulations in the HF population. Particularly, the assumption of equivalent safety remains highly uncertain and may be inappropriate as ferric carboxymaltose is associated with a risk of hypophosphatemia that may require additional monitoring and treatment, as detailed in the product monograph.[2] If hypophosphatemia has a nonnegligible quality of life impact in patients with HF, a cost-utility analysis would have been the preferred approach for the pharmacoeconomic analysis.

The sponsor submitted a cost-minimization analysis assuming equivalent clinical efficacy and safety between ferric carboxymaltose, iron sucrose, and ferric derisomaltose. In the submission, ferric carboxymaltose was associated with cost savings of $15 and $394 per patient per treatment course when compared to ferric derisomaltose and iron sucrose, respectively, at public list price. However, the costs of monitoring and treating hypophosphatemia were not included by the sponsor. CDA-AMC did not undertake a base-case

reanalysis as the limitations identified by CDA-AMC could not be addressed given that they were related to the underlying assumption of equivalent clinical efficacy and safety between ferric carboxymaltose and its comparators, and the variability of the administration of the total iron dose per treatment course. A scenario analysis was conducted that included monitoring and treatment costs based on assumptions and expert opinion for nonsevere hypophosphatemia. This analysis estimated that cost savings would be reduced (incremental savings = $3 compared to ferric derisomaltose and $382 compared to iron sucrose); however, if rates of hypophosphatemia requiring treatment and monitoring are higher than assumed (10% based on expert opinion) or if patients develop more severe adverse events (e.g., severe hypophosphatemia, hypophosphatemic osteomalacia, and/or fractures), savings associated with the reimbursement of ferric carboxymaltose for the reimbursement population may be further reduced or eliminated. Due to the remaining uncertainty concerning the comparative safety across iron products and its associated costs, the magnitude of cost savings associated with ferric carboxymaltose remains uncertain. All costs and incremental savings are further based on publicly available list prices and may not reflect actual prices paid by Canadian public drug plans.

Note that as any potential cost savings are entirely driven by reduced administration costs (nurse time, infusion chair time, and infusion devices consumed), they would not be achieved from a public drug plan perspective as they may pertain to a different budget holder.

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Appendix 1: Cost Comparison Table

Please note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts and drug plans. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 4: CDA-AMC Cost Comparison Table for the Treatment of Iron Deficiency in Adults With HF and NYHA Class II or Class III to Improve Exercise Capacity

Treatment	Strength	Form	Price	Recommended dosage[a]	Average drug cost per treatment course ($)[a]
Recommended use					
Ferric carboxymaltose (Ferinject)	**50 mg/mL**	**100 mg/2 mL** **500 mg/10 mL** **1,000 mg/20 mL** **Single-use vial for IV infusion**	**$45.0000** **$225.0000** **$450.0000**	**500 mg to 2,000 mg[c]** **A single infusion should not exceed 15mg/kg or 1,000 mg. Additional infusion should be a minimum of 7 days apart.** **Minimum infusion time: no minimal to 15 minutes (dose dependent)** **In adults with HDD-CKD a single infusion should not exceed 200 mg per hemodialysis session.**	**$225 to $900**
Actual practice (off-label use)					
Ferric derisomaltose (Monoferric)	100 mg/mL	100 mg/1 mL 500 mg/5 mL 1,000 mg/10 mL Vial for IV infusion	45.0000 225.0000[11] 450.0000[11]	Health Canada has not authorized use for treatment of ID in HF For adults (> = 18 years): 500 mg to 2,000 mg[c] A single infusion should not exceed 20mg/kg or 1,500 mg. Additional infusions should be a minimum of 7 days. Minimum infusion time: 20 minutes (≤ 1,000 mg) to 30 minutes (> 1,000 mg). 500 mg doses can be given as IV bolus.	$225 to $900
Iron sucrose (generic)	20 mg/mL	100 mg/5 mL	27.5000	Health Canada has not authorized use for treatment of ID in HF without CKD Adults with NDD-CKD: 1,000 mg cumulative dose,	$275

Treatment	Strength	Form	Price	Recommended dosage[a]	Average drug cost per treatment course ($)[a]
				100 mg at a time (5 sessions) over a 14-day period Adults with HDD-CKD patients: 1,000 mg cumulative dose, 100 mg at a time per consecutive hemodialysis session Adults with PDD-CKD patients: 1,000 mg cumulative dose, 2 infusions of 300 mg each 14 days apart, followed by a 400 mg infusion 14 days later	
Sodium ferric gluconate complex (Ferrlecit)[d]	12.5 mg/mL	62.5 mg/5 mL vial for IV infusion	28.3000[e]	For patients aged 1 to 17: Health Canada has not authorized use for pediatric patients Adults with HDD-CKD: Most patients will require a minimum total iron need of 1,000 mg, 125 mg at a time per consecutive hemodialysis session administered over 1 hour. A single infusion should not exceed 12.5 mg/min.	$453 or more

CKD = chronic kidney disease; HDD = hemodialysis dependent; NDD = nondialysis-dependent; PDD = peritoneal dialysis dependent.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 21, 2024),[18] unless otherwise indicated, and do not include dispensing fees. Ferrlecit is indicated for the treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy. The expert consulted by CDA-AMC did not consider Ferrlecit a key comparator.

[a]Recommended doses vary depending on the combination of weight and hemoglobin levels, supporting tables available in the product monograph.

[c]The lower range is the recommended dose for a patient weighing 35 kg and with a hemoglobin of ≥ 14 g/dL and the upper range is the recommended dose for a patient weighing 70 kg with a hemoglobin of < 10 g/dL, per the recommended dose for the treatment of iron deficiency anemia.

[l]Indicated for the treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy. The expert consulted by CDA-AMC did not consider Ferrlecit a key comparator.

[e]Saskatchewan formulary, accessed August 8, 2024.[21]

Additional Details on the CDA-AMC Reanalyses and Additional Analyses

Table 5: Scenario Analysis Conducted on the Sponsor's Base Case — Probabilistic

Drug	Total drug costs ($)	Incremental drug costs ($)	Total costs ($)	Incremental costs ($)
Sponsor's base case				
Ferric carboxymaltose	725	Reference	852	Reference
Ferric derisomaltose	725	—	867	−15
Iron sucrose	443	282	1,246	−394
CDA-AMC exploratory analysis, including monitoring and treatment costs of hypophosphatemia				
Ferric carboxymaltose[a]	731	Reference	857	Reference

Drug	Total drug costs ($)	Incremental drug costs ($)	Total costs ($)	Incremental costs ($)
Ferric derisomaltose	719	12	860	−3
Iron sucrose	440	292	1,240	−382

[a]Assuming 10% of patients were tested and treated (symptomatic). Components added to the total drug cost: 2 laboratory tests (L194) from the Ontario Schedule of Benefits for Laboratory Services,[22] one general consultation visit (A005) from the Ontario Schedule of Benefits: Physician Services,[23] price of sodium phosphate from the Alberta formulary assuming a full bottle (20 tablets) is dispensed per patient.[24]

Appendix 2: Submitted Budget Impact Analysis and CDA-AMC Appraisal

Please note that this appendix has not been copy-edited.

Table 6: Summary of Key Take-Aways

Key take-aways of the budget impact analysis
• CDA-AMC identified the following key limitations from the sponsor's analysis: ◦ Use of a claims-based approach to estimate market size and market shares introduces uncertainty. ◦ Market capture of ferric carboxymaltose is uncertain. ◦ Dispensing and markup fees were included in the sponsor submission. ◦ The submitted model was not user-friendly and unnecessarily complicated. • CDA-AMC did not conduct a base-case analysis, due to uncertainties surrounding the sponsor's submitted model. CDA-AMC did not present any scenario or exploratory analyses. The sponsor's base case suggested the reimbursement of ferric carboxymaltose would result in a 3-year budgetary impact of $404,491.

Summary of Sponsor's Budget Impact Analysis

In the submitted budget impact analysis (BIA), the sponsor assessed the expected budget impact of reimbursing ferric carboxymaltose injection for the treatment of ID in adult patients with HF and NYHA class II or class III to improve exercise capacity.[25] The BIA was conducted from the perspective of the Canadian public drug plans over a three-year horizon (2025/26 to 2027/28) with 2024/25 as the base year, using a claims-based approach. Claims data in outpatient setting and sales volume (in mg) in inpatient setting were obtained from IQVIA PHARMASTAT (Q1 2019 to Q3 2023) and IQVIA Canadian Drugstore and Hospital Purchase Audit databases, respectively, (January 2019 to September 2023) for ferric derisomaltose and iron sucrose.[25] Both inpatient and outpatient future market sizes were based on the extrapolation of the historical data using linear regression. In the outpatient setting, the market shares of the different iron products were calculated as their proportional number of claims. In the inpatient setting, the market shares of the different iron products were calculated as their proportional sales volume of 100mg vials. In the new drug scenario, the sponsor assumed claim-to-claim and vial-to-vial displacement between ferric carboxymaltose and comparators, and captures rates proportional to the shares of the 2 comparators in the reference scenario. The sponsor's pan-Canadian estimates reflect the aggregated results of outpatient and inpatient estimates from provincial drug plans (excluding Quebec), as well as the Non-Insured Health Benefits program. Key inputs to the BIA are documented in Table 7.

The following key assumptions were made by the sponsor:

- The sponsor-submitted model assumed that the introduction of ferric carboxymaltose would not lead to any expansion of IV iron products in the pan-Canadian market.
- The sponsor assumed the proportion of claims and sales volume of 100mg vials specific to HF was 1.7% of the total n. claims and total sales volume, and the remaining (98.3%) is used for IDA, according to internal data on file.

- The uptake of FCM was based on internal market calculations for the FCM sales in the European Union (1%, 3% and 9% in years 1 to 3), and assumed to be the same in inpatient and outpatient settings, across all jurisdictions.
- The sponsor assumed the average dose per treatment course for the HF population was 1,605.5 mg (i.e., cumulative iron dose to achieve total iron need).
- In the outpatient setting, to calculate drug costs and administration costs, the sponsor assumed a claim was equivalent to 1 treatment course.
- In the inpatient setting, to calculate drug costs, the sponsor multiplied the number of 100mg vials by their specific costs; and to calculate administration costs, the sponsor divided the number of 100mg vials by the average dose per treatment course (1,605.5 mg).

Table 7: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3 if appropriate)
Target Population[a]	
Number of claims (i.e., treatment courses), outpatient	643 / 756 / 869
Volume (in 100mg vials), inpatient	50,634 /51,359 /52,084
Market Uptake (3 years)[a]	
Reference scenario	
Outpatient	
Ferric derisomaltose	100% / 100% / 100%
Iron sucrose	0% / 0% / 0%
Inpatient	
Ferric derisomaltose	3% / 3% / 4%
Iron sucrose	97% / 97% / 96%
New drug scenario	
Outpatient	
Ferric carboxymaltose	1% / 3% / 9%
Ferric derisomaltose	99% / 97% / 91%
Iron sucrose	0% / 0% / 0%
Inpatient	
Ferric carboxymaltose	1% / 3% / 9%
Ferric derisomaltose	3% / 3% / 3%
Iron sucrose	96% / 84% / 88%
Cost of treatment course[a]	
Inpatient	

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3 if appropriate)
Cost per 100mg vial (and average treatment course)	
Ferric carboxymaltose	$45.00
Ferric derisomaltose	$45.00
Iron sucrose	$27.50
Outpatient	
Cost per claim (i.e., average treatment course)	
Ferric carboxymaltose	$765.00
Ferric derisomaltose	$765.00
Iron sucrose	$467.50

[a]The parameters are for Ontario. The sponsor estimated different market share for other jurisdictions.

Note: average dose per treatment course for the HF population was 1,605.5 mg. This dose was used to determine the cost of a treatment course.

Summary of the Sponsor's BIA Results

The sponsor's estimated budget impact of funding ferric carboxymaltose for the treatment of ID in adult patients with HF and NYHA class II or class III to improve exercise capacity resulted in an incremental budgetary impact of $29,207 in year 1, $91,164 in year 2, $284,120 in year 3, for a 3-year total incremental budget impact of $404,491 ($7,369 in the outpatient setting and $397,122 in the inpatient setting).

CDA-AMC Appraisal of the Sponsor's BIA

CDA-AMC identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Use of a claims-based approach to estimate market size and market shares introduces uncertainty with the anticipated budget impact of ferric carboxymaltose:** The sponsor estimated the current market size based on the number of outpatient claims and inpatient sales volume (of 100 mg vials) using historic public claims data for ferric derisomaltose and iron sucrose. The sponsor extrapolated the historical claims data using linear regression to project the future market size without consideration of system capacity (i.e., outpatient clinics and inpatient settings), changes in the number of patients with coverage by the drug plans, and potential shifts from inpatient utilization to outpatient utilization. As claims data reflects only patients who had access to coverage for the comparators, a significant portion of the population who may have ID and HF but did not have access to the IV iron products in the past (unless meeting criteria for IDA treatment) would be excluded from future projections.

  Additionally, the sponsor assumed that inpatient administration of iron therapy is covered by all jurisdictions under the drug plan perspective. However, differences between jurisdictional funding exist, where some jurisdictions would cover inpatient administration of iron therapy, others may only fund for patients with specific indications (e.g., CKD) and some others do not reimburse inpatient iron

therapy. As we are unable to isolate these subpopulations from the claims, the inclusion of inpatient claims in the pan-Canadian estimates from a drug plan perspective is uncertain, as they may pertain to a different budget holder.

Further, the sponsor assumed claim-to-claim and vial-to-vial displacement between ferric carboxymaltose and comparators in outpatient and inpatient settings, respectively. The sponsor also assumed that a single claim represented 1 full treatment course. However, there are differences in the maximum dose per single infusion between ferric carboxymaltose and comparators and it is uncertain whether a single claim truly includes all the infusions required to deliver a treatment course (i.e., 1 cumulative iron dose) or if it represents a maximum iron dose allowed per single infusion. The sponsor did not obtain the number of patients from claims and sales data which would have been more appropriate to estimate the number of patients eligible for the drug under review, given the differences in dosing frequencies and durations between treatments. For example, assuming an adult patient with HF requires chronic treatment with iron sucrose, this patient can only access a maximum of 4.7 treatment courses throughout the year (5 weekly infusions and reassessment after 4 weeks post final administration to allow adequate time for erythropoiesis and iron utilization); while if being treated with ferric derisomaltose, the same patient can access a maximum of approximately 8.6 treatment courses throughout the year (1 single infusion and reassessment after 4 weeks). Therefore, it is uncertain if treatment with ferric carboxymaltose will displace the same number of claims or treatment courses for the same average patient over time.

Finally, the sponsor's approach of estimating market share based on historic claims-based data are problematic given recent changes in the treatment guidelines. The 2023 guideline published by the European Society of Cardiology found that ferric derisomaltose should also be recommended to treat ID in adult patients with HF, along with ferric carboxymaltose.[1] However, iron sucrose was not included in the guidelines for this population. The claims-based data reflects outdated practices and fails to account for new therapeutic preferences and standards. Consequently, estimating market share based on historical data may not represent the future treatment landscape. This misalignment may have led to inaccurate future market share assumptions of ferric derisomaltose and iron sucrose, ultimately adding uncertainty to the estimated budget impact.[1]

    - CDA-AMC was unable to address this limitation.

Additional limitations were identified in the following but were not addressed by CDA-AMC as the limitation pertaining to the claims-based approach cannot be addressed:

- **Market uptake of ferric carboxymaltose is uncertain:** The sponsor's assumption that ferric carboxymaltose has a share of 9% in both the inpatient and outpatient settings is likely underestimated. Clinical expert feedback obtained by CDA-AMC highlighted that it is unlikely that iron sucrose, if currently used, may continue as a preferred treatment for ID in adult patients with HF (due to recent changes in guidelines[1,17]) and that the uptake of ferric carboxymaltose is likely to be higher. In turn, the estimated budget impact may not accurately reflect the pan-Canadian landscape.

- **Dispensing and markup fees are included for individuals receiving outpatient treatment:** The sponsor included a dispensing fee and pharmacy markup in the estimation of cost per claim for all treatments. Dispensing fees and markups vary across jurisdictions; however, the sponsor did not incorporate jurisdiction-specific fees for Ontario, New Brunswick, Nova Scotia, and Prince Edward Island. Consequently, the estimated budget impact may not accurately reflect the actual costs incurred by public health care payers.
- **The sponsor's submitted model for the budget impact model is not user-friendly and unnecessarily complicated:** Several of the model inputs and assumptions in the sponsor's submitted budget impact model were difficult to test or modify with alternate inputs or assumptions due to unnecessary complexity (i.e., inconsistency between sheets; recalculation of jurisdictional budget impact does not feed into the pan-Canadian results sheet).

CDA-AMC Reanalyses of the BIA

In the absence of more reliable estimates to inform the key parameters of the BIA, the sponsor's submitted case was maintained (Table 8). CDA-AMC expects that the budget impact of reimbursement of ferric carboxymaltose for the treatment of ID in adult patients with HF and NYHA class II or class III to improve exercise capacity will be sensitive to more reliable inputs which may affect the market size calculation, uptake and displacement of comparators by ferric carboxymaltose and the prices of treatments for ID paid for by the public drug plans.

Table 8: Detailed Breakdown of the CDA-AMC Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation) ($)	Year 1 ($)	Year 2 ($)	Year 3 ($)	Three-year total ($)
Submitted base case	Reference	NA	5,850,247	6,252,646	6,655,189	18,758,082
	New drug	NA	5,879,454	6,343,809	6,939,310	19,162,573
	Budget impact	NA	29,207	91,164	284,120	404,491
Submitted base case, outpatient	Reference	NA	673,435	787,338	901,242	2,362,015
	New drug	NA	673,938	788,966	906,480	2,369,384
	Budget impact	NA	503	1,627	5,238	7,369
Submitted base case, inpatient	Reference	NA	5,063,710	5,332,273	5,600,980	15,996,963
	New drug	NA	5,092,414	5,421,809	5,879,862	16,394,085
	Budget impact	NA	28,704	89,536	278,882	397,122

BIA = budget impact analysis; NA = estimates for base year were not available within the sponsor's submitted model

Note: Reference year costs are not available in the submitted model. The sponsor included the reference year number of claims and vials, but did not calculate the budget for the reference year.

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.