### Title

Hypophosphataemia risk associated with ferric carboxymaltose in heart failure: A pooled analysis of clinical trials




### Journal

ESC Heart Failure, 10(2)

### ISSN

2055-5822



### Authors

Rosano, Giuseppe MC
Kalantar-Zadeh, Kamyar
Jankowska, Ewa A



### Publication Date

2023-04-01

### DOI

10.1002/ehf2.14286

Peer reviewed

ESC HEART FAILURE
*ESC Heart Failure* 2023; **10**: 1294–1304
Published online 1 February 2023 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14286

ORIGINAL ARTICLE

# Hypophosphataemia risk associated with ferric carboxymaltose in heart failure: A pooled analysis of clinical trials

Giuseppe MC Rosano[1]*, Kamyar Kalantar-Zadeh[2] and Ewa A. Jankowska[3]

[1]*Department of Medical Sciences, IRCCS San Raffaele Roma, Rome, Italy;* [2]*Division of Nephrology and Hypertension and Kidney Transplantation, University of California, Irvine, California, USA; and* [3]*Institute of Heart Diseases, Wrocław Medical University, Wrocław, Poland*

## Abstract

**Aims** Iron deficiency is a common finding among patients with heart failure (HF) and is associated with adverse outcomes, including decreased quality of life, increased risk of hospitalization, and decreased survival. Intravenous ferric carboxymaltose (FCM) has been shown to improve outcomes among patients with HF and concomitant iron deficiency, but FCM is associated with an increased risk of hypophosphataemia. We aimed to better characterize this risk among HF populations.

**Methods and results** This pooled analysis examined data from 41 studies of adults with iron deficiency across disease states and therapeutic areas. Among the 7931 patients treated with FCM available for analysis, 14% made up the HF subgroup. Additional subgroups included women's health (36%), non–dialysis-dependent chronic kidney disease (NDD-CKD; 27%), haemodialysis-dependent chronic kidney disease (HD-CKD; 1%), gastrointestinal (10%), neurology (3%), and other (10%). The incidence of post-baseline moderate or severe hypophosphataemia (i.e. serum phosphate [$PO_4^{3-}$] level $<$2.0 mg/dL) varied across the therapeutic areas, with the lowest incidences observed in the HD-CKD (0%), HF (8.1%), and NDD-CKD (12.8%) subgroups. The prevalence of moderate or severe hypophosphataemia among the women's health, other, gastrointestinal, and neurology subgroups was 30.1%, 40.6%, 51.0%, and 55.6%, respectively. In the HF subgroup, one patient ($<$0.1%) had a serum $PO_4^{3-}$ of $<$1.0 mg/dL recorded, compared with 4.8% and 4.0% of the subjects in the neurology and gastrointestinal groups, respectively. With the exception of the HD-CKD subgroup, mean serum $PO_4^{3-}$ levels decreased through weeks 2 to 4, and then returned toward baseline and plateaued by week 8. The strongest predictor of hypophosphataemia was preserved kidney function (estimated glomerular filtration rate: $>$60 mL/min/1.73 $m^2$ vs. $<$30 mL/min/1.73 $m^2$; odds ratio: 12.2). Among patients in the HF subgroup, the incidence of treatment-emergent adverse events potentially related to hypophosphataemia (e.g. cardiac failure, ventricular tachyarrhythmias, fatigue, muscle weakness, bone pain, neurological symptoms, and muscle pain) was lower among FCM-treated patients than among those receiving placebo, and lower among patients with a post-baseline $PO_4^{3-}$ $<$2 mg/dL vs. those not meeting such criteria.

**Conclusions** The risk of laboratory-assessed hypophosphataemia in HF patients treated with FCM was lower than that seen in patients in other therapeutic areas treated with FCM, and clinical events associated with hypophosphataemia are uncommon with FCM therapy in this population. Appropriate monitoring, particularly soon after administration in the unlikely event of repeated dosing in HF patients, will allow for further refinement of management strategies. [Correction added on 24 February 2023, after first online publication: In the preceding sentence, "…administration, will allow…" has been corrected to "…administration in the unlikely event of repeated dosing in HF patients, will allow…" in this version.]

**Keywords** Hypophosphataemia; Ferric carboxymaltose; Heart failure; Intravenous; Chronic kidney disease

*Received: 30 August 2022; Revised: 30 November 2022; Accepted: 9 January 2023*
**Correspondence to: Giuseppe M.C. Rosano, Centre for Clinical and Basic Research, IRCCS San Raffaele Roma, Via della Pisana 235, 00163 Rome, Italy. Phone: +39 06 52252409; Fax: +39 06 52252465. Email: giuseppe.rosano@gmail.com*

## Introduction

Iron deficiency is a common complication of numerous underlying pathologies and is encountered across a spectrum of specialties.[1] Functional or absolute iron deficiency occurs frequently among patients with chronic kidney disease (CKD), cancer, and systemic inflammatory conditions, including inflammatory bowel disease.[2] Iron deficiency is also observed among patients with restless leg syndrome and among women with a history of heavy menstrual bleeding or during the peripartum period.[3–5]

Iron deficiency is also a common finding among patients with heart failure (HF).[6–10] The presence of iron deficiency in the setting of HF, independent of anaemia, is associated with adverse outcomes, including reduced exercise capacity, decreased quality of life, increased risk of hospitalization, and increased cardiovascular and all-cause mortality.[9,11–16] Current guidelines recommend that periodic screening for iron deficiency be conducted and that ferric carboxymaltose (FCM) be considered for symptomatic patients with HFrEF and documented iron deficiency (i.e. serum ferritin $<$100 ng/mL or serum ferritin 100–299 ng/mL with transferrin saturation [TSAT] $<$ 20%) and for patients recently hospitalized for HF with iron deficiency to alleviate HF symptoms, improve exercise capacity and quality of life, and reduce hospitalizations.[10] Although multiple intravenous iron preparations are available to clinicians,[17] FCM is the most studied in patients with HF, and the only preparation included in the European Society of Cardiology HF guidelines.[10] The recommendation to consider FCM was based, in part, on the efficacy and safety results of numerous randomized controlled trials of FCM in HF populations.[18–21]

Iron-induced hypophosphataemia was first reported 40 years ago,[22] and, while not uniquely associated with FCM, the risk is greater with FCM than other intravenous iron formulations.[23–26] FCM induces a temporary increase in intact fibroblast growth factor 23 (iFGF23), supressing phosphate ($PO_4^{3-}$) reabsorption and vitamin D activity, and ultimately causing increased $PO_4^{3-}$ excretion and reduced serum $PO_4^{3-}$ levels.[27,28] Hypophosphataemia is frequently asymptomatic unless patients develop severe or rapid reductions in serum $PO_4^{3-}$, but it can impact the musculoskeletal system (e.g. muscle weakness, rhabdomyolysis, impaired diaphragm function, and acute respiratory failure), present as neurological disturbances (e.g. paraesthesia, confusion, dysarthria, seizures, or coma), and have haematologic consequences (e.g. haemolysis, leukocyte dysfunction, defective clot retraction, and thrombocytopaenia).[29] Cardiac manifestations, including ventricular arrhythmias and myocardial dysfunction, have also been described as potential consequences of hypophosphataemia.[30–32]

Although the risk of hypophosphataemia associated with FCM has been examined in numerous cohorts,[23–26] the risk of this complication among patients with HF—a population with unique FCM dosing needs, underlying pathophysiology, and co-morbidities—has been incompletely characterized.[33,34] The aim of this analysis was to evaluate the incidence of laboratory-defined hypophosphataemia in studies of FCM conducted in HF populations compared with patients with other underlying disorders.

## Methods

This retrospective analysis was based on pooled data from all FCM studies—across all disease states—sponsored by Vifor Pharma and its licensing partners, through a data lock point of 28 April 2021. Studies were included if they were conducted in adult populations and post-baseline serum $PO_4^{3-}$ levels were available. Included study populations were classified based on the primary therapeutic area examined: HF, gastrointestinal (largely inflammatory bowel disease), non–dialysis-dependent CKD (NDD-CKD), haemodialysis-dependent CKD (HD-CKD), neurology (i.e. restless leg syndrome), women's health (i.e. peripartum and heavy menstrual bleeding), and other (i.e. iron deficiency anaemia, oncology, peritoneal dialysis–dependent CKD, surgery, other bleeding disorder, and unknown or multifactorial reasons for iron deficiency).

Serum $PO_4^{3-}$ levels were defined according to Common Terminology Criteria for Adverse Events (CTCAE) thresholds (v4.0) and severity definitions (v5.0).[35,36] Serum $PO_4^{3-}$ concentrations of at least 2.5 mg/dL (and $<$4.5 mg/dL) were considered normal. Hypophosphataemia was defined as serum $PO_4^{3-}$ levels below 2.5 mg/dL and was further categorized as mild (2.0 to $<$2.5 mg/dL), moderate (1 to $<$2.0 mg/dL), and severe ($<$1 mg/dL).

Analyses were performed on two distinct data sets. The pooled FCM analysis set was defined as all subjects who received at least one FCM administration and had at least one post-baseline serum $PO_4^{3-}$ assessment available for analysis. To further characterize the safety of FCM in HF, a pooled HF analysis set included all subjects from HF studies who received at least one administration of FCM, placebo, or comparator (i.e. intravenous iron sucrose or standard medical care) and had at least one post-baseline serum $PO_4^{3-}$ measurement. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Serum $PO_4^{3-}$ levels and change from baseline (i.e. the last non-missing result on or before treatment start) were summarized by study therapeutic area. For each patient, the lowest post-baseline serum $PO_4^{3-}$ level (i.e. nadir) was categorized and summarized. A stepwise logistic regression of post-baseline moderate or severe hypophosphataemia (serum $PO_4^{3-}$ $<$ 2.0 mg/dL) was performed. Variables considered to be potential confounders or effect modifiers of the possible relationship between FCM and hypophosphataemia

**Table 1** Baseline characteristics of the pooled FCM analysis set

| | GI (*N* = 792) | HF (*N* = 1074) | NDD-CKD (*N* = 2107) | HD-CKD (*N* = 70) | Neuro (*N* = 248) | Women's health (*N* = 2839) | Other (*N* = 801) | Total (*N* = 7931) |
|---|---|---|---|---|---|---|---|---|
| Female (%) | 67.4 | 44.8 | 63.4 | 50.0 | 74.2 | 100.0 | 84.5 | 76.7 |
| Age (year), mean (SD) | 46.4 (17.18) | 68.7 (10.72) | 67.2 (12.98) | 54.6 (14.24) | 53.1 (14.23) | 33.4 (9.56) | 49.7 (17.69) | 50.9 (19.69) |
| Race (%) | | | | | | | | |
| White | 79.3 | 96.7 | 59.9 | 3.0 | 70.2 | 38.5 | 52.4 | 58.5 |
| Black or African American | 7.8 | 0.5 | 23.5 | 37.1 | 4.8 | 30.0 | 17.9 | 20.1 |
| Asian | 8.3 | 2.4 | 2.3 | 0 | 0.8 | 11.0 | 12.5 | 7.0 |
| BMI (kg/m$^2$), mean (SD) | 26.43 (6.991) | 28.04 (5.213) | 32.30 (8.401) | 32.05 (8.095) | 28.50 (6.573) | 29.69 (7.598) | 28.22 (7.878) | 29.68 (7.738) |
| Haemoglobin (g/dL), mean (SD) | 10.1 (1.67) | 12.3 (1.49) | 10.3 (0.83) | 11.3 (0.80) | 13.4 (1.37) | 9.8 (1.55) | 10.1 (1.39) | 10.5 (1.66) |
| Haemoglobin category (%) | | | | | | | | |
| <12 g/dL | 90.4 | 40.1 | 99.4 | 77.1 | 13.3 | 93.5 | 94.5 | 85.0 |
| ≥12 g/dL | 9.6 | 59.8 | 0.6 | 22.9 | 86.7 | 6.5 | 5.5 | 15.0 |
| Missing | 0 | <0.1 | <0.1 | 0 | 0 | 0 | 0 | <0.1 |
| Ferritin (mcg/L), mean (SD) | 19.3 (35.22) | 69.7 (60.65) | 76.3 (67.89) | 219.3 (138.74) | 47.7 (43.62) | 16.7 (21.99) | 83.0 (177.47) | 49.4 (80.72) |
| Ferritin category (%) | | | | | | | | |
| <30 mcg/L | 83.0 | 27.1 | 29.0 | 5.7 | 42.3 | 84.6 | 64.5 | 57.8 |
| 30 to <100 mcg/L | 14.6 | 53.9 | 44.0 | 15.7 | 48.0 | 14.4 | 14.9 | 28.7 |
| ≥100 mcg/L | 2.1 | 18.9 | 27.1 | 78.6 | 9.7 | 0.9 | 20.6 | 13.4 |
| Missing | 0.3 | <0.1 | 0 | 0 | 0 | <0.1 | 0 | <0.1 |
| $PO_4^{3-}$ (mg/dL), mean (SD) | 3.7 (1.37) | 4.0 (8.92) | 4.1 (0.84) | 5.5 (1.97) | 3.5 (0.55) | 3.8 (0.66) | 3.7 (0.78) | 3.9 (3.36) |
| $PO_4^{3-}$ category (%) | | | | | | | | |
| <1 mg/dL | 0 | 0 | 0 | 1.4 | 0 | 0 | 0 | <0.1 |
| 1 to <2 mg/dL | 0.5 | 0 | <0.1 | 0 | 0.8 | 0.2 | 0.4 | 0.2 |
| 2 to <2.5 mg/dL | 2.7 | 2.0 | 0.6 | 4.3 | 2.8 | 1.5 | 3.0 | 1.7 |
| 2.5 to <4.5 mg/dL | 87.9 | 87.2 | 71.2 | 21.4 | 91.9 | 83.0 | 86.6 | 81.0 |
| ≥4.5 mg/dL | 8.6 | 8.6 | 27.4 | 72.9 | 4.4 | 15.2 | 10.0 | 16.5 |
| Missing | 2.1 | 2.1 | 0.7 | 0 | 0 | 0.1 | 0 | 0.6 |
| TSAT (%), mean (SD) | 9.6 (8.76) | 17.2 (12.00) | 18.9 (8.68) | 22.3 (11.65) | 22.6 (10.26) | 9.8 (8.29) | 14.7 (12.07) | 14.3 (10.49) |
| TSAT category (%) | | | | | | | | |
| <20% | 89.0 | 72.8 | 56.9 | 37.1 | 42.7 | 88.6 | 72.5 | 74.6 |
| ≥20% | 10.6 | 26.6 | 42.5 | 62.9 | 57.3 | 7.1 | 26.1 | 23.5 |
| Missing | 0.4 | 0.6 | 0.6 | 0 | 0 | 4.3 | 1.4 | 2.0 |
| eGFR (CKD-EPI; mL/min/1.73 m$^2$), mean (SD) | 92.4 (28.90) | 60.0 (21.63) | 31.7 (15.71) | 12.5 (21.15) | 88.9 (19.69) | 115.8 (19.48) | 88.1 (32.00) | 77.7 (41.02) |
| eGFR (mL/min/1.73 m$^2$) category (%) | | | | | | | | |
| ≤30 | 3.8 | 8.7 | 51.9 | 94.3 | 0 | 0.1 | 5.2 | 16.7 |
| >30 to ≤45 | 3.3 | 17.9 | 31.4 | 1.4 | 0.8 | <0.1 | 5.4 | 11.7 |
| >45 to ≤60 | 4.5 | 20.9 | 11.9 | 0 | 4.4 | 0.3 | 6.5 | 7.4 |
| >60 | 84.7 | 46.9 | 4.8 | 4.3[a] | 71.0 | 90.3 | 73.4 | 58.1 |
| Missing | 3.7 | 5.6 | 0 | 0 | 23.8 | 9.1 | 9.5 | 6.1 |

Abbreviations: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; FCM, ferric carboxymaltose; GI, gastrointestinal; HD-CKD, haemodialysis-dependent chronic kidney disease; HF, heart failure; NDD-CKD, non–dialysis-dependent chronic kidney disease; $PO_4^{3-}$, phosphate; TSAT, transferrin saturation.

[a]Although categorized as HD-CKD in the present and earlier analyses, three of the patients in this study did not have end-stage kidney disease.

included: sex; race; age group (≤60, >60 to ≤70, >70 to ≤80, >80 years); baseline body mass index category (underweight [<18.5 kg/m$^2$], normal [18.5–24.9 kg/m$^2$], overweight [25–29.9 kg/m$^2$], or obese [≥30 kg/m$^2$]); baseline haemoglobin category (i.e. anaemic [<12 g/dL] or non-anaemic [≥12 g/dL]); baseline ferritin category (<30, 30 to <100, or ≥100 mcg/L); baseline TSAT (<20% or ≥20%); and baseline estimated glomerular filtration rate (eGFR) based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (≤30, >30 to ≤45, >45 to ≤60, or >60 mL/min/1.73 m$^2$). The impact of exposure to FCM treatment was also examined as assessed by: cumulative FCM dose (<1000, 1000 to <1500, or ≥1500 mg iron), maximal single dose (≤500, >500 to ≤750, or >750 mg iron), and the number of FCM administrations.

Reported TEAEs were analysed to identify safety signals potentially related to hypophosphataemia. Cardiology TEAEs that could be related to hypophosphataemia were captured with Standardized Medical Dictionary for Regulatory Activities [MedDRA] Queries (SMQ) for 'cardiac failure' and 'ventricular tachyarrhythmias'. We also examined the rates of general symptoms that could be related to hypophosphataemia, including the following MedDRA Preferred Terms: fatigue, muscle weakness, bone pain, neurological symptoms, muscle pain, white cell dysfunction, haemolysis, cardiac failure, and ventricular tachyarrhythmias.

# Results

A total of 52 studies were identified in the clinical database; 41 of these studies enrolled adults and had post-baseline $PO_4^{3-}$ data available, and therefore were included in the present analyses (*Table S1*). Assessment of $PO_4^{3-}$ levels was dictated by study protocol but approximately one-quarter of the studies (containing approximately one-third of the total patients) did not have an assessment at week 1 and/or week 2. Among the six HF studies, the earliest post-baseline assessment of serum of $PO_4^{3-}$ levels occurred at week 4 in two studies and at week 6 in three studies.

## Pooled FCM analysis

In total, 7931 patients from 41 clinical trials were included in the pooled FCM analysis set. Patients included in the women's health, NDD-CKD, and HF subgroups accounted for approximately 36%, 27%, and 14% of the FCM analysis set, respectively. At baseline, 85% of patients were anaemic, with mean serum ferritin of 49.4 mcg/L and mean TSAT of 14.3%, and all but 2% had serum $PO_4^{3-}$ values of 2.5 mg/dL or greater. Additional baseline characteristics are summarized in *Table 1*.

Across the FCM analysis set, the mean (SD) cumulative FCM dose received by patients was 1333 (532) mg. Overall, 38% of patients received a single dose of FCM, ranging from 19% of the NDD-CKD subgroup to 100% of the HD-CKD subgroup. Additional information regarding FCM dosing is summarized in *Table S2*.

Changes in mean serum $PO_4^{3-}$ are plotted by disease state/therapeutic area in *Figure 1*. With the exception of the HD-CKD subgroup, mean serum $PO_4^{3-}$ levels decreased through weeks 2 to 4, and subsequently returned toward baseline and plateaued by week 8. Mean $PO_4^{3-}$ levels reached their nadir at week 2 for most subgroups, but decreased until week 4 among the HF population. The nadir mean (SD) $PO_4^{3-}$ levels were similar between NDD-CKD (week 2: 3.14 [1.14] mg/dL) and HF populations (week 4: 3.15 [0.91] mg/dL), and were higher than those observed for the gastrointestinal, neurology, women's health, and other subgroups. Patients in the neurology subgroup exhibited the lowest mean (SD) $PO_4^{3-}$ level during follow-up (1.79 [0.61] mg/dL).

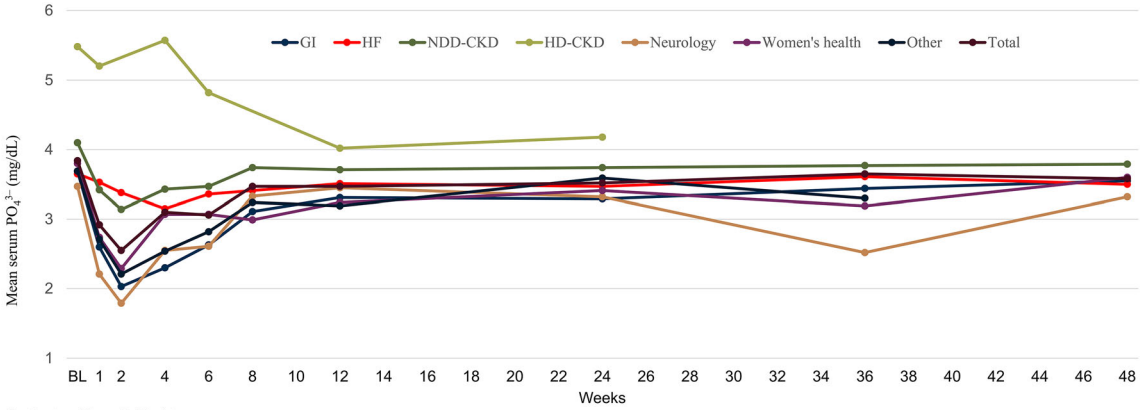
The incidence of post-treatment moderate or severe hypophosphataemia (i.e. serum $PO_4^{3-}$ level <2.0 mg/dL) varied across the therapeutic areas, with the lowest incidences observed in the HD-CKD (0%), HF (8.1%), and NDD-CKD (12.8%) subgroups. The prevalence of moderate or severe hypophosphataemia among the women's health, other, gastrointestinal, and neurology subgroups was 30.1%, 40.6, 51.0%, and 55.6% respectively (*Figure 2*). Based on the stepwise multiple regression analysis, normal or mildly impaired kidney disease (i.e. eGFR >60 mL/min/1.73 m$^2$) was the strongest predictor for severe or moderate hypophosphataemia (*Table 2*). The incidence of moderate or severe hypophosphataemia was significantly lower in the HF subgroup compared with the women's health, gastrointestinal, neurology, and other subgroups (odds ratios [95% confidence interval]: 4.01 [2.89, 5.57], 11.68 [8.44, 16.17], 28.61 [16.40, 49.90], and 9.65 [6.82, 13.65], respectively).

Across all subgroups, severe hypophosphataemia (i.e. serum $PO_4^{3-}$ < 1.0 mg/dL) was observed in 99 patients (1.2%) at any point during follow-up. In the HF subgroup, one patient (<0.1%) met criteria for severe hypophosphataemia, compared with 4.8% and 4.0% of the subjects in the neurology and gastrointestinal groups, respectively.

## Pooled HF analysis

Six clinical trials (FER-CARS-01, FER-CARS-02 [FAIR-HF], FER-CARS-03 [EFFICACY-HF], FER-CARS-04 [EFFECT-HF], FER-CARS-05 [CONFIRM-HF], and FER-CARS-06 [AFFIRM-AHF]) with a total of 1993 patients, were included in the pooled HF analysis set. Of the included patients, 53.9% ($n$ = 1074) were treated with intravenous FCM, 40.6% ($n$ = 809) received placebo, and 5.5% ($n$ = 110) received comparator therapy (i.e. intravenous iron sucrose or standard medical care). At base-

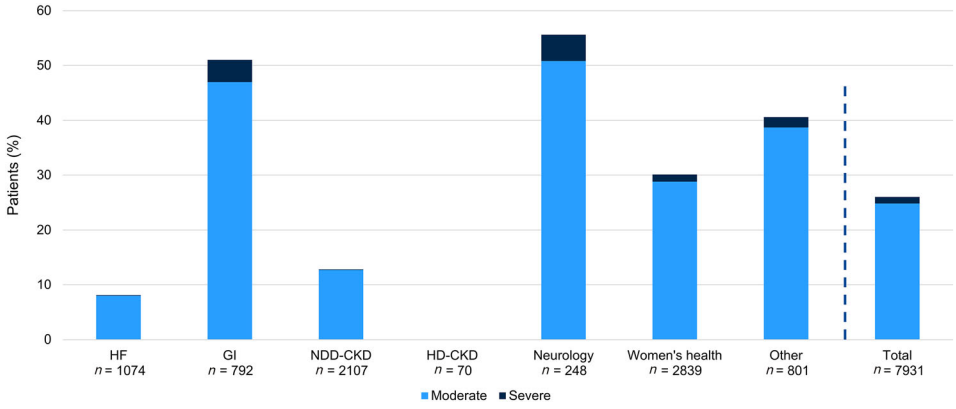
**Figure 1** Mean serum $PO_4^{3-}$ levels at baseline and during FCM treatment in the pooled FCM analysis set. BL, baseline; FCM, ferric carboxymaltose; GI, gastrointestinal; HD-CKD, haemodialysis-dependent chronic kidney disease; HF, heart failure; NDD-CKD, non–dialysis-dependent chronic kidney disease; $PO_4^{3-}$, phosphate.




Number of patients with available data

| | BL | 1 | 2 | 4 | 6 | 8 | 12 | | 24 | 36 | 48 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| GI | 787 | 686 | 548 | 515 | 258 | 340 | 303 | | 144 | 101 | 60 |
| HF | 1049 | 34 | 35 | 318 | 671 | 105 | 974 | | 910 | 155 | 460 |
| NDD-CKD | 2093 | 1361 | 1401 | 1942 | 111 | 1646 | 455 | | 400 | 357 | 314 |
| HD-CKD | 70 | 19 | 0 | 45 | 70 | 0 | 4 | | 4 | 0 | 0 |
| Neurology | 248 | 185 | 141 | 90 | 144 | 75 | 75 | | 104 | 10 | 92 |
| Women's health | 2836 | 1596 | 1214 | 2000 | 1324 | 527 | 231 | | 17 | 7 | 3 |
| Other | 801 | 717 | 469 | 412 | 409 | 176 | 115 | | 70 | 1 | 0 |
| Total | 7884 | 4598 | 3808 | 5322 | 2924 | 2869 | 2157 | | 1649 | 631 | 929 |

**Figure 2** Proportion of patients in the pooled FCM analysis set meeting criteria for moderate or severe hypophosphataemia during FCM treatment. Serum $PO_4^{3-}$ levels were defined according to CTCAE thresholds (v4.0) and severity definitions (v5.0) as follows: normal, 2.5 to <4.5 mg/dL; mild decrease, 2.0 to <2.5 mg/dL; moderate, 1 to <2.0 mg/dL; severe, <1 mg/dL. CTCAE, Common Terminology Criteria for Adverse Events; FCM, ferric carboxymaltose; GI, gastrointestinal; HD-CKD, haemodialysis-dependent chronic kidney disease; HF, heart failure; NDD-CKD, non–dialysis-dependent chronic kidney disease; $PO_4^{3-}$, phosphate.




line, 40.3% of all subjects in this analysis set were anaemic, and 95.7% had documented baseline serum $PO_4^{3-}$ levels of 2.5 mg/dL or greater (*Table S3*). More than half of the HF analysis set had renal impairment as assessed by a baseline eGFR of 60 mL/min/1.73 $m^2$ or less.

As previously described, among FCM-treated patients with HF, $PO_4^{3-}$ reduction was most pronounced at week 4, and levels returned toward baseline values thereafter (*Figure 3A*). Whereas patients in the comparator group demonstrated similar temporal reductions in $PO_4^{3-}$ levels, the magnitude of these changes was less than those observed with FCM. At week 4, patients receiving placebo demonstrated virtually no change in mean serum $PO_4^{3-}$ levels (*Figure 3B*). By week 12, there was little numerical difference between


DOI: 10.1002/ehf2.14286

**Table 2** Risk factors for developing severe or moderate hypophosphataemia in the pooled FCM analysis set

| Factor | Step 1 *P* value | Step 2 *P* value | Step 3 *P* value | Odds ratio [95% CI] |
|---|---|---|---|---|
| Age (10 years increase) | <0.0001 | <0.0001 | <.0001 | 1.111 [1.066, 1.158] |
| Sex: Female vs. male | <0.0001 | 0.5681 | | |
| BMI (overall effect) | <0.0001 | <0.0001 | <.0001 | |
| BMI: Underweight vs. normal | | | | 1.440 [0.965, 2.148] |
| BMI: Overweight vs. normal | | | | 0.741 [0.635, 0.865] |
| BMI: Obese vs. normal | | | | 0.518 [0.445, 0.604] |
| Baseline haemoglobin (10 g/dL increase) | <0.0001 | 0.0019 | 0.0012 | 0.523 [0.353, 0.774] |
| eGFR (overall effect) | <0.0001 | <0.0001 | <.0001 | |
| eGFR: 30 to ≤45 mL/min/1.73 $m^2$ vs. ≤30 mL/min/1.73 $m^2$ | | | | 2.529 [1.886, 3.392] |
| eGFR: 45 to ≤60 mL/min/1.73 $m^2$ vs. ≤30 mL/min/1.73 $m^2$ | | | | 5.084 [3.743, 6.904] |
| eGFR: >60 mL/min/1.73 $m^2$ vs. ≤30 mL/min/1.73 $m^2$ | | | | 12.233 [9.407, 15.909] |
| Baseline TSAT (10% increase)[a] | <0.0001 | | | |
| Baseline ferritin (10 mcg/L increase) | <0.0001 | <0.0001 | <0.0001 | 0.972 [0.962, 0.981] |
| FCM multiple dose vs. FCM single dose | <0.0001 | <0.0001 | <0.0001 | 3.029 [2.203, 4.165] |
| FCM cumulative dose (mg) (overall effect) | <0.0001 | 0.0196 | 0.0198 | |
| FCM cumulative dose: 1000 mg to ≤1500 mg vs. ≤1000 mg | | | | 1.496 [1.106, 2.024] |
| FCM cumulative dose: >1500 mg vs. ≤1000 mg | | | | 1.297 [0.952, 1.767] |
| FCM maximum single dose (mg) (overall effect) | <0.0001 | <0.0001 | <0.0001 | |
| FCM maximum single dose: >500 mg to ≤750 mg vs. ≤500 mg | | | | 2.143 [1.742, 2.636] |
| FCM maximum single dose: >750 mg vs. ≤500 mg | | | | 1.178 [0.953, 1.456] |

*Note*: Results represent stepwise logistic regression of post-baseline moderate or severe hypophosphataemia (serum $PO_4^{3-}$ level <2.0 mg/dL), including the factors listed in the table, unless stated otherwise. Analysis steps were as follows: Step 1: Univariate logistic regression performed for each factor. Step 2: Multivariate logistic regression performed for all factors for which the *P* value in step 1 was ≤0.20. Step ≥3: Multivariate logistic regression performed excluding the factor that had the highest *P* value in the previous step if it was >0.10. Last step: When the *P* values of all factors included in the model were ≤0.10. The odds ratio and its 95% CI for the selected significant factors are provided.

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR; estimated glomerular filtration rate; FCM, ferric carboxymaltose; $PO_4^{3-}$, phosphate; TSAT, transferrin saturation.

[a]TSAT was excluded from the stepwise logistic regression due to multicollinearity with baseline ferritin.

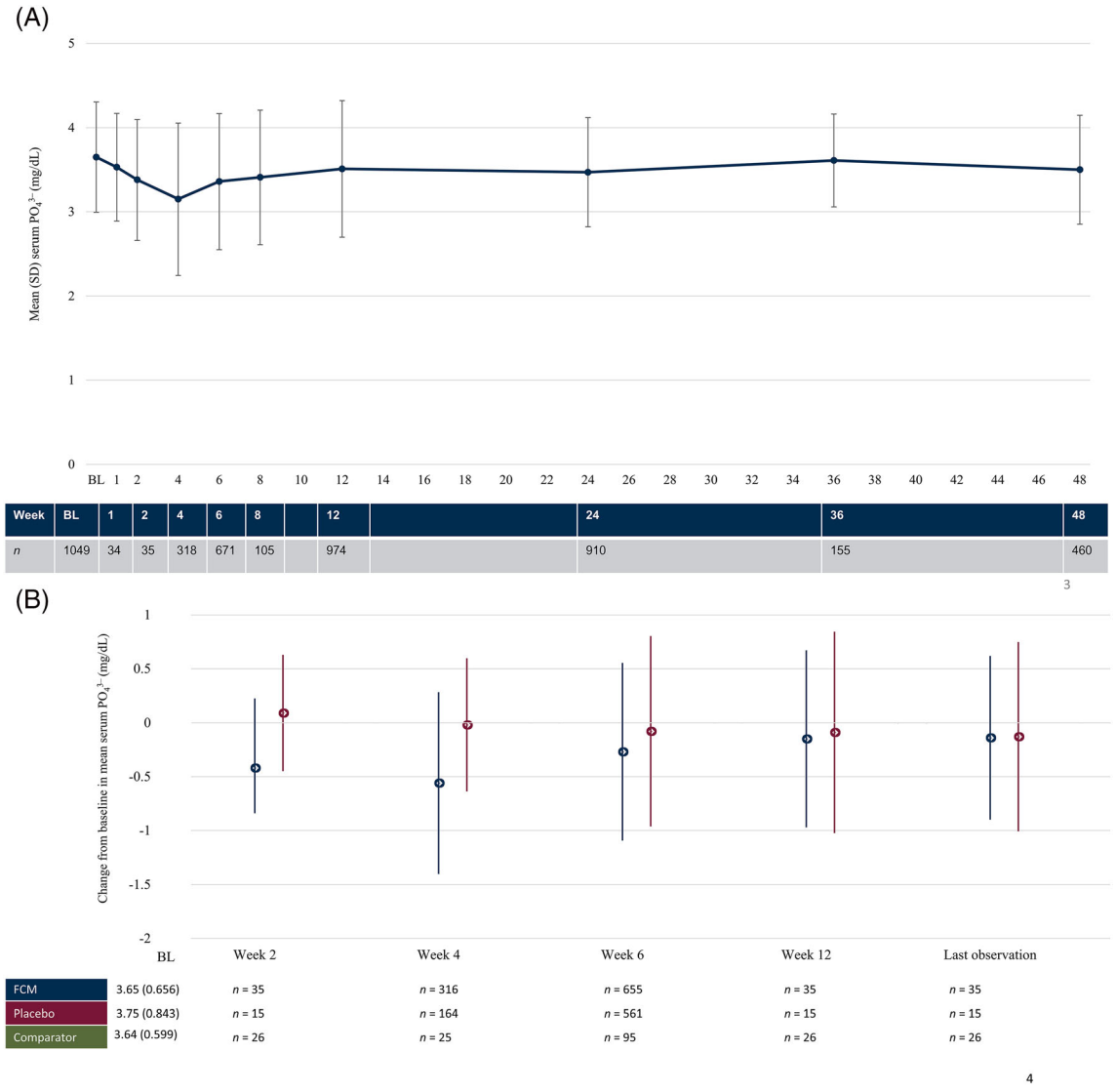
$PO_4^{3-}$ values across the treatment groups. As summarized in *Table S4*, the studies utilized one of the two general dosing schemes; in three studies, iron repletion was calculated with the Ganzoni formula, and maintenance iron was administered to all patients, and in three studies, iron repletion was based on screening weight and haemoglobin, and maintenance iron was administered only if iron deficiency reappeared or persisted. In the two 52 week trials, more than 75% of patients received only one or two IV iron infusions.

The rates of potential hypophosphataemia-related TEAEs were examined in patients with and without at least one post-baseline serum $PO_4^{3-}$ level below 2 mg/dL. Overall, 91 patients in the pooled HF analysis set (FCM: 83; placebo: 5; comparator: 3) had a post-baseline $PO_4^{3-}$ level <2 mg/dL. Among those patients, cardiology-specific TEAEs potentially associated with hypophosphataemia occurred in 14.5% of those receiving FCM (*n* = 12), compared with 20% receiving placebo (*n* = 1) and 0% receiving a comparator (*n* = 0) (*Figure 4*, left). In the same population, TEAEs that could be related to hypophosphataemia were reported by 16.9% of patients receiving FCM (*n* = 14), 20% of those receiving placebo (*n* = 1), and 0% of those receiving a comparator (*n* = 0). Nearly 90% of patients in the pooled HF analysis set (*n* = 1780) did not have a recorded $PO_4^{3-}$ concentration <2 mg/dL. Among those patients, cardiology-specific hypophosphataemia symptom TEAEs occurred in 22.2% receiving FCM (*n* = 207), 31.4% receiving placebo (*n* = 233), and 16.8% receiving a comparator (*n* = 18; *Figure 4*, right). TEAEs considered potential manifestations of hypophosphataemia occurred in 26.1% of those receiving FCM (*n* = 243), 34.8% of those receiving placebo (*n* = 258), and 19.6% of those receiving a comparator (*n* = 21).

## Discussion

It is well established that hypophosphataemia is a common occurrence following the administration of FCM. As such, it is recommended that serum $PO_4^{3-}$ levels be monitored in patients who receive multiple administrations and those with existing risk factors for hypophosphataemia.[37,38] The results of the present analysis are consistent with these prior recommendations. However, as observed in HF studies,[18–21] frequent dosing of FCM is generally not needed to replenish iron levels. As we will further discuss, this is likely protective against severe and prolonged hypophosphataemia. Approximately one-quarter of patients across all indications receiving FCM experienced at least one serum $PO_4^{3-}$ level <2 mg/dL during follow-up. Severe reductions in serum $PO_4^{3-}$ levels were rare, observed in 1.2% of all patients in the analysis. The observation that hypophosphataemia was predicted by multiple doses of FCM and higher maximum doses of FCM further supports current recommendations for monitoring.

**Figure 3** (A) Mean serum $PO_4^{3-}$ levels at baseline and during FCM treatment, and (B) mean changes in serum $PO_4^{3-}$ levels across treatment groups in the pooled HF analysis set. BL, baseline; FCM, ferric carboxymaltose; HF, heart failure; $PO_4^{3-}$, phosphate.

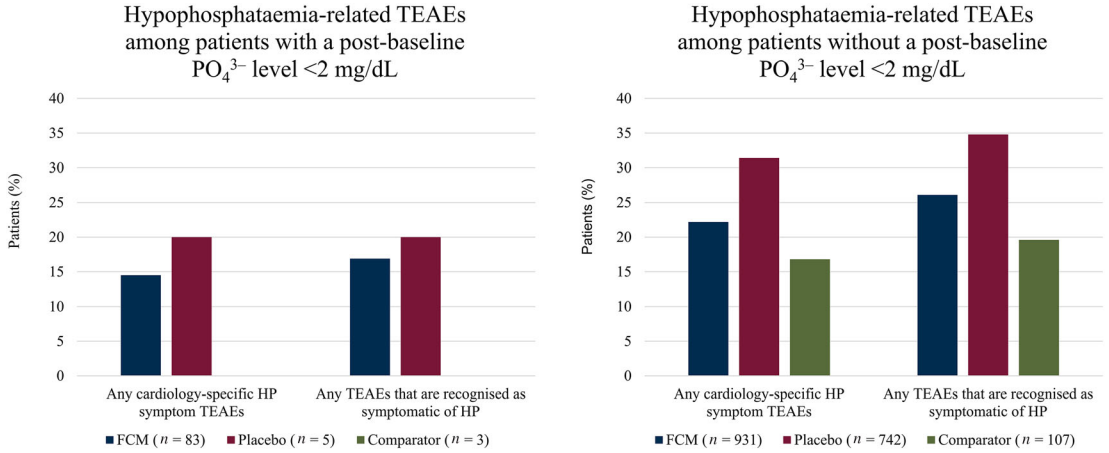



Reductions in serum $PO_4^{3-}$ levels generally occurred soon after dosing and spontaneously returned toward baseline after 4 weeks.

We observed that serum $PO_4^{3-}$ levels consistent with moderate to severe hypophosphataemia were less common among patients with HF than among the other disease states/therapeutic areas examined (with the exception of HD-CKD). Fewer than 10% of FCM-treated patients in the HF subgroup had serum $PO_4^{3-}$ levels of $<2$ mg/dL observed, and only one patient ($<0.1\%$) had a serum $PO_4^{3-}$ level $<1$ mg/dL (at week 4). Moreover, when mean serum $PO_4^{3-}$ levels were examined, the magnitude of reductions in patients with HF were less than those observed in patients with gastrointestinal, neurological, or women's health conditions leading to iron deficiency/iron deficiency anaemia. The magnitude of serum $PO_4^{3-}$ decreases observed in HF populations were similar to those seen in NDD-CKD populations.

A number of factors may account for the lower risk of hypophosphataemia observed in the HF subgroup relative to most of the other subgroups examined. The dosing of FCM differed across subgroups. Patients receiving FCM in the HF subgroup received an average of 4.3 doses of FCM, nearly twice the number given to other subgroups. The relatively small (but frequent) doses of FCM in FAIR-HF (i.e. 200 mg weekly until iron repletion was achieved and then every 4 weeks as needed) likely contributed to this finding.[18] In the 1-year AFFIRM-AHF trial, more than three-quarters of

**Figure 4** Treatment-emergent adverse events that can be manifestations of hypophosphataemia (pooled HF analysis set). FCM, ferric carboxymaltose; HF, heart failure; HP, hypophosphataemia; $PO_4^{3-}$, phosphate; TEAE, treatment-emergent adverse event.




patients required only one to two doses of FCM during the 24 week treatment period.[21] The highest FCM doses used among patients in the HF group were marginally lower than those administered to other subgroups (with the exception of HD-CKD). Most notably, kidney function was impaired in most patients with HF (mean [SD] eGFR: 60.0 [21.63] mL/min/1.73 $m^2$). In contrast, renal impairment was relatively rare in the other non-CKD subgroups.

Our finding that many patients with HF have a reduced eGFR is consistent with findings from prior studies.[39–41] Although traditionally considered a complication of end-stage kidney disease, studies have demonstrated that patients with earlier stages of CKD exhibit disordered phosphate metabolism and are at increased risk of hyperphosphataemia.[42–44] As such, patients with HF and concomitant renal impairment may be less prone to the development of below-normal serum $PO_4^{3-}$ levels. The relative 'protection' against hypophosphataemia conferred by renal impairment was demonstrated in our risk prediction models: patients with an eGFR above 60 mL/min/1.73 $m^2$ were 12-fold more likely to develop hypophosphataemia than patients with an eGFR below 30 mL/min/1.73 $m^2$. In summary, although regularly receiving higher cumulative FCM doses, often as a result of higher doses administered less frequently, patients with HF developed hypophosphataemia less frequently than most of the non-HF subgroups examined.

Beyond laboratory measures of serum $PO_4^{3-}$ levels, our analysis found no evidence of an increase in clinical manifestations of hypophosphataemia. In fact, patients treated with FCM reported lower rates of the specified TEAEs than patients who received placebo. Moreover, these events were no more common among patients with documented moderate or severe hypophosphataemia than among those patients not meeting such laboratory criteria. Such comparisons should be viewed in the context of the very low number of patients treated with placebo meeting criteria for laboratory-assessed hypophosphataemia (i.e. $n$ = 5).

The findings of the present analysis are largely consistent with data examining the risk of hypophosphataemia in other HF cohorts. In a single-centre trial of 23 patients with HFrEF, a single 1000 mg dose of FCM resulted in significant reductions in mean serum $PO_4^{3-}$ levels among patients with a preserved eGFR (i.e. >60 mL/min/1.73 $m^2$) of approximately 1 mg/dL.[34] Mean serum $PO_4^{3-}$ levels reached their lowest levels 14 days after infusion and returned to baseline by week 4. In contrast, no significant reductions in serum $PO_4^{3-}$ were observed in patients with HF and concomitant CKD. Overall, serum $PO_4^{3-}$ levels transiently below 2.5 mg/dL were observed in approximately 60% of patients. The more frequent assessment of serum $PO_4^{3-}$ levels by Stöhr and colleagues[34] may have contributed to the higher prevalence of hypophosphataemia than that observed in the current analysis. In the present analysis, fewer than 5% of patients had available laboratory assessments at weeks 1 or 2; transient hypophosphataemia that resolved by week 4 or 6 would not have been captured.

More recently, Dashwood *et al*. examined the risk of hypophosphataemia among 173 inpatients with stabilized HFrEF who were administered FCM for the management of iron deficiency.[33] With most patients receiving daily blood draws while hospitalized and less frequently after discharge, 27% experienced hypophosphataemia (<2 mg/dL). The incidence of 'severe' (~1.25 to 2 mg/dL) and 'extreme' (~ < 1.25 mg/dL) hypophosphataemia was 25% and 2%, respectively. Serum $PO_4^{3-}$ levels reached their lowest level at approximately 1 week and returned to normal at 6 weeks. The authors reported that one of the patients with a serum $PO_4^{3}$ level <1.25 mg/dL experienced bone pain and muscle weakness. As in the present analysis, impaired kidney function was protective against the development of hypophosphataemia.

The present analysis represents the largest assessment of the risk of hypophosphataemia associated with FCM among HF patients enrolled in randomized clinical trials. The retrospective design of the study must be considered when interpreting the results. Importantly, the heterogeneity across study design and duration, patient characteristics, and limited data available at early time points should be considered when evaluating the data. Because there was no standardized approach to serum $PO_4^{3-}$ monitoring across the 41 studies, and most of the HF-specific studies did not include early (i.e. before week 4) assessments, we likely missed the 'true' nadir of serum $PO_4^{3-}$ levels. In the HF trials, fewer than 7% of patients had a serum $PO_4^{3-}$ level reported within 2 weeks of their first FCM dose. Despite this shortcoming, the available data strongly suggest that the risk of clinically relevant hypophosphataemia is very low among HF populations vs. that observed in other populations. The risk for hypophosphataemia after FCM treatment appears to be mitigated by decreased kidney function, a common co-morbidity among patients with HF. It is expected that large, ongoing trials of FCM including HEART-FID[45] and FAIR-HF2[46] will further clarify the risk of hypophosphataemia in HF populations receiving FCM. Because the recently-completed IRONMAN study, a randomized controlled trial of ferric derisomaltose in patients with HF and iron deficiency, did not include assessment of $PO_4^{3-}$ concentrations, no comparison regarding the risk of hypophosphataemia in HF populations treated with different iron preparation can be made.[47] It is worth noting that the use of ferric derisomaltose is not without a risk for development of hypophosphataemia.[48,49]

In summary, our analyses found that the incidence of hypophosphataemia in HF patients treated with FCM was lower than that seen in patients in other therapeutic areas. This reduced risk is likely the result of suboptimal kidney function and impaired renal excretion of phosphate, a common co-morbidity among patients with HF. When present, laboratory-assessed hypophosphataemia was generally not associated with clinical sequelae associated with severe hypophosphataemia. Appropriate monitoring, particularly soon after administration in the unlikely event of repeated dosing in HF patients, will allow for further refinement of management strategies.

## Acknowledgement

Assistance with the writing and editing of the manuscript was provided by Adam Perahia, MD, of NorthStar Strategic Consulting, LLC.

## Conflict of interest

EAJ reports speaker advisory honoraria from Vifor Pharma outside of the submitted work and received an unrestricted grant from Vifor Pharma for Wrocław Medical University outside of the submitted work; KK-Z reports honoraria from Abbott, AbbVie, ACI Clinical, Akebia, Alexion, Amgen, Ardelyx, AstraZeneca, Aveo, B. Braun, Cara Therapeutics, Chugai, Cytokinetics, Daiichi Sankyo, DaVita, Fresenius, Genentech, Haymarket Media, Hospira, Kabi, Keryx, Kissei, Novartis, Pfizer, Regulus, Relypsa, Resverlogix, Sandoz, Sanofi, Dr Schaer, Shire, UpToDate, Vifor, and ZS Pharma; GR reports no conflicts of interest.

## Funding

GMCR was supported by funding of the Italian Ministry of Health (Ricerca Corrente: 20/1819). This analysis describes research funded by Vifor Pharma and partners. Vifor Pharma provided funding for writing and editing services to assist with the preparation of this manuscript. [Correction added on 24 February 2023, after first online publication: The first line of the Funding statement has been changed from "This work was…Corrente: RRC 2022 23680775 and…" to "GMCR was… Corrente: 20/1819" in this version.]

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Studies included in the pooled analysis ($n$ = 41).
**Table S2.** FCM dosing characteristics in the pooled FCM analysis set.
**Table S3.** Baseline characteristics in the pooled HF analysis set.
**Table S4.** FCM dosing in HF studies.

## References

1. Peyrin-Biroulet L, Williet N, Cacoub P. Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review. *Am J Clin Nutr*. 2015; **102**: 1585–1594.
2. Cappellini MD, Comin-Colet J, de Francisco A, Dignass A, Doehner W, Lam CS, Macdougall IC, Rogler G, Camaschella C, Kadir R, Kassebaum NJ, Spahn DR, Taher AT, Musallam KM, IRON CORE Group. Iron deficiency

across chronic inflammatory conditions: international expert opinion on definition, diagnosis, and management. *Am J Hematol*. 2017; **92**: 1068–1078.
3. Trenkwalder C, Allen R, Högl B, Clemens S, Patton S, Schormair B, Winkelmann J. Comorbidities, treatment, and pathophysiology in restless legs syndrome. *Lancet Neurol*. 2018; **17**: 994–1005.
4. Mégier C, Peoc'h K, Puy V, Cordier AG. Iron metabolism in normal and pathological pregnancies and fetal consequences. *Metabolites*. 2022; **12**: 129.
5. Fraser IS, Mansour D, Breymann C, Hoffman C, Mezzacasa A, Petraglia F. Prevalence of heavy menstrual bleeding and experiences of affected women in a European patient survey. *Int J Gynaecol Obstet*. 2015; **128**: 196–200.
6. Beale AL, Warren JL, Roberts N, Meyer P, Townsend NP, Kaye D. Iron deficiency in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Open Heart*. 2019; **6**: e001012.
7. Rocha BML, Cunha GJL, Menezes Falcão LF. The burden of iron deficiency in heart failure: therapeutic approach. *J Am Coll Cardiol*. 2018; **71**: 782–793.
8. von Haehling S, Gremmler U, Krumm M, Mibach F, Schön N, Taggeselle J, Dahm JB, Angermann CE. Prevalence and clinical impact of iron deficiency and anaemia among outpatients with chronic heart failure: the PrEP registry. *Clin Res Cardiol*. 2017; **106**: 436–443.
9. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, Lok DJ, Rosentryt P, Torrens A, Polonski L, van Veldhuisen DJ, van der Meer P, Jankowska EA. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J*. 2013; **165**: 575–582.e3.
10. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021; **42**: 3599–3726.
11. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, von Haehling S, Doehner W, Banasiak W, Polonski L, Filippatos G, Anker SD, Ponikowski P. Iron deficiency predicts impaired exercise capacity in patients with systolic chronic heart failure. *J Card Fail*. 2011; **17**: 899–906.
12. Enjuanes C, Klip IT, Bruguera J, Cladellas M, Ponikowski P, Banasiak W, van Veldhuisen DJ, van der Meer P, Jankowska EA, Comín-Colet J. Iron deficiency and health-related quality of life in chronic heart failure: results from a multicenter European study. *Int J Cardiol*. 2014; **174**: 268–275.
13. Martens P, Nijst P, Verbrugge FH, Smeets K, Dupont M, Mullens W. Impact of iron deficiency on exercise capacity and outcome in heart failure with reduced, mid-range and preserved ejection fraction. *Acta Cardiol*. 2018; **73**: 115–123.
14. Marchi G, Busti F, Vianello A, Girelli D. Anemia and iron deficiency in heart failure: extending evidences from chronic to acute setting. *Intern Emerg Med*. 2021; **16**: 167–170.
15. Suciadi LP, Henrina J, Putra ICS, Cahyadi I, Gunawan HFH. Chronic heart failure: clinical implications of iron homeostasis disturbances revisited. *Cureus*. 2022; **14**: e21224.
16. Graham FJ, Masini G, Pellicori P, Cleland JGF, Greenlaw N, Friday J, Kazmi S, Clark AL. Natural history and prognostic significance of iron deficiency and anaemia in ambulatory patients with chronic heart failure. *Eur J Heart Fail*. 2022; **24**: 807–817.1.
17. Schaefer B, Meindl E, Wagner S, Tilg H, Zoller H. Intravenous iron supplementation therapy. *Mol Aspects Med*. 2020; **75**: 100862.
18. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P, FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009; **361**: 2436–2448.
19. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD, CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†. *Eur Heart J*. 2015; **36**: 657–668.
20. van Veldhuisen DJ, Ponikowski P, van der Meer P, Metra M, Böhm M, Doletsky A, Voors AA, Macdougall IC, Anker SD, Roubert B, Zakin L, Cohen-Solal A, EFFECT-HF Investigators. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. *Circulation*. 2017; **136**: 1374–1383.
21. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, Fabien V, Filippatos G, Göhring UM, Keren A, Khintibidze I, Kragten H, Martinez FA, Metra M, Milicic D, Nicolau JC, Ohlsson M, Parkhomenko A, Pascual-Figal DA, Ruschitzka F, Sim D, Skouri H, van der Meer P, Lewis BS, Comin-Colet J, von Haehling S, Cohen-Solal A, Danchin N, Doehner W, Dargie HJ, Motro M, Butler J, Friede T, Jensen KH, Pocock S, Jankowska EA, AFFIRM-AHF investigators. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet*. 2020; **396**: 1895–1904.
22. Okada M, Imamura K, Fuchigami T, Omae T, Iida M, Nanishi F, Murakami M, Ohgushi H, Yao T, Fujita K, Ogawa K. 2 cases of nonspecific multiple ulcers of the small intestine associated with osteomalacia caused by long-term intravenous administration of saccharated ferric oxide. *Nippon Naika Gakkai Zasshi*. 1982; **71**: 1566–1572.
23. Rosano G, Schiefke I, Göhring UM, Fabien V, Bonassi S, Stein J. A pooled analysis of serum phosphate measurements and potential hypophosphataemia events in 45 interventional trials with ferric carboxymaltose. *J Clin Med*. 2020; **9**: 3587.
24. Bellos I, Frountzas M, Pergialiotis V. Comparative risk of hypophosphatemia following the administration of intravenous iron formulations: a network meta-analysis. *Transfus Med Rev*. 2020; **34**: 188–194.
25. Glaspy JA, Lim-Watson MZ, Libre MA, Karkare SS, Hadker N, Bajic-Lucas A, Strauss WE, Dahl NV. Hypophosphatemia associated with intravenous iron therapies for iron deficiency anemia: a systematic literature review. *Ther Clin Risk Manag*. 2020; **16**: 245–259.
26. Schaefer B, Tobiasch M, Wagner S, Glodny B, Tilg H, Wolf M, Zoller H. Hypophosphatemia after intravenous iron therapy: comprehensive review of clinical findings and recommendations for management. *Bone*. 2022; **154**: 116202.
27. Blumenstein I, Shanbhag S, Langguth P, Kalra PA, Zoller H, Lim W. Newer formulations of intravenous iron: a review of their chemistry and key safety aspects – hypersensitivity, hypophosphatemia, and cardiovascular safety. *Expert Opin Drug Saf*. 2021; **20**: 757–769.
28. Erben RG. Physiological actions of fibroblast growth factor-23. *Front Endocrinol (Lausanne)*. 2018; **9**: 267.
29. Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. *Am J Med*. 2005; **118**: 1094–1101.
30. Schwartz A, Brotfain E, Koyfman L, Kutz R, Gruenbaum SE, Klein M, Zlotnik A. Association between hypophosphatemia and cardiac arrhythmias in the early stage of sepsis: could phosphorus replacement treatment reduce the incidence of arrhythmias? *Electrolyte Blood Press*. 2014; **12**: 19–25.
31. Ariyoshi N, Nogi M, Ando A, Watanabe H, Umekawa S. Hypophosphatemia-induced cardiomyopathy. *Am J Med Sci*. 2016; **352**: 317–323.

32. Ognibene A, Ciniglio R, Greifenstein A, Jarjoura D, Cugino A, Blend D, Whittier F. Ventricular tachycardia in acute myocardial infarction: the role of hypophosphatemia. *South Med J*. 1994; **87**: 65–69.
33. Dashwood A, Vale C, Laher S, Chui F, Hay K, Wong YW. Hypophosphatemia is common after intravenous ferric carboxymaltose infusion among patients with symptomatic heart failure with reduced ejection fraction. *J Clin Pharmacol*. 2021; **61**: 515–521.
34. Stöhr R, Sandstede L, Heine GH, Marx N, Brandenburg V. High-dose ferric carboxymaltose in patients with HFrEF induces significant hypophosphatemia. *J Am Coll Cardiol*. 2018; **71**: 2270–2271.
35. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed 15 March 2022.
36. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Accessed 15 March 2022.
37. Injectafer [package insert]. Shirley, NY: American Regent, Inc.; February 2022.
38. Ferinject [summary of product characteristics]. Staines-upon-Thames, UK: Vifor Pharma UK Limited; November 2021. https://www.medicines.org.uk/emc/product/5910/smpc. Accessed 15 March 15, 2022.
39. Löfman I, Szummer K, Hagerman I, Dahlström U, Lund LH, Jernberg T. Prevalence and prognostic impact of kidney disease on heart failure patients. *Open Heart*. 2016; **3**: e000324.
40. Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J*. 2015; **36**: 1437–1444.
41. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation*. 2004; **109**: 1004–1009.
42. Vikrant S, Parashar A. Prevalence and severity of disordered mineral metabolism in patients with chronic kidney disease: a study from a tertiary care hospital in India. *Indian J Endocrinol Metab*. 2016; **20**: 460–467.
43. Ketteler M. Phosphate metabolism in CKD stages 3–5: dietary and pharmacological control. *Int J Nephrol*. 2011; **2011**: 970245.
44. Chartsrisak K, Vipattawat K, Assanatham M, Nongnuch A, Ingsathit A, Domrongkitchaiporn S, Sumethkul V, Distha-Banchong S. Mineral metabolism and outcomes in chronic kidney disease stage 2–4 patients. *BMC Nephrol*. 2013; **14**: 14.
45. Mentz RJ, Ambrosy AP, Ezekowitz JA, Lewis GD, Butler J, Wong YW, De Pasquale CG, Troughton RW, O'Meara E, Rockhold FW, Garg J, Samsky MD, Leloudis D, Dugan M, Mundy LM, Hernandez AF, HEART-FID Trial Investigators. Randomized placebo-controlled trial of ferric carboxymaltose in heart failure with iron deficiency: rationale and design. *Circ Heart Fail*. 2021; **14**: e008100.
46. U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03036462 Last updated October 21, 2021. Accessed November 5, 2022.
47. Kalra PR, Cleland JGF, Petrie MC, Thomson EA, Kalra PA, Squire IB, Ahmed FZ, Al-Mohammad A, Cowburn PJ, Foley PWX, Graham FJ, Japp AG, Lane RE, Lang NN, Ludman AJ, Macdougall IC, Pellicori P, Ray R, Robertson M, Seed A, Ford I, IRONMAN Study Group. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. *Lancet*. 2022; **S0140-6736**: 2083–2089 [Epub ahead of print].
48. Wong KY, Yu KY, Mak MWH, Lee KM, Lee KF. Intravenous iron isomaltoside (Monofer)-induced hypophosphataemia: a case report. *Hong Kong Med J*. 2022; **28**: 267–269.
49. Zoller H, Wolf M, Blumenstein I, Primas C, Lindgren S, Thomsen LL, Reinisch W, Iqbal T. Hypophosphataemia following ferric derisomaltose and ferric carboxymaltose in patients with iron deficiency anaemia due to inflammatory bowel disease (PHOSPHARE-IBD): a randomised clinical trial. *Gut*. 2022: gutjnl-2022-327897 [Epub ahead of print].


*[Correction added on 24 February 2023, after first online publication: New reference 36 was added to the Reference list. Reference numbers and their citations were renumbered in this version.]*